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Temporal Trends in the Risk of Multiple Primary Cancers and Competing Mortality among Adult-Onset Cancer Patients

by

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(Medical Research)

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Statement of Originality

This thesis contains no material which has been accepted for a degree or diploma by the University or any other institution, except by way of background information and duly acknowledged in the thesis, and to the best of my knowledge and belief no material previously published or written by another person except where due acknowledgement is made in the text of the thesis, nor does the thesis contain any material that infringes copyright.

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Statement of Co-Authorship

This thesis includes chapters for which Yuanzi Ye (YY) is not the sole author. YY was the first author in the research of each manuscript; she was assisted by the co-authors. The contributions of each author are acknowledged below.

Chapters 3:

Ye Y, Neil AL, Wills KE, Venn AJ. Temporal trends in the risk of developing multiple primary cancers: a systematic review. *BMC Cancer.* 2016; 16: 849.

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We the undersigned agree with the above stated “proportion of work undertaken” for each of the above published peer-reviewed manuscripts contributing to this thesis:

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Date:	10/09/2018	29/11/2018

Statement of Ethical Conduct

The research associated with this thesis abides by the international and Australian codes on human and animal experimentation, the guidelines by the Australian Government's Office of the Gene Technology Regulator and the rulings of the Safety, Ethics and Institutional Biosafety Committees of the University.

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Abstract

Background: Cancer patients are at risk of developing multiple primary cancers (MPCs). MPCs and non-cancer events compete with first cancers as the cause of death. This thesis aims to investigate temporal trends in the risk of MPCs and competing mortality due to MPCs and non-cancer events among adult-onset cancer patients in Tasmania.

Methods: A systematic review of temporal trends in the risk of MPCs was performed. Original data were extracted from the population-based Tasmanian Cancer Registry in Australia. Patients with a first cancer registered between 1980-2009 were followed for incident second cancers to 2013 and for deaths to 2014. For non-cancer mortality, patients with a first cancer registered between 2006-2013 were followed up to 2015. MPC risks were quantified and trends in MPC risk were assessed in multivariable Poisson models. Mortality due to MPCs and non-cancer events were assessed in competing risk models.

Results: The systematic review indicated an increasing trend in the risk of MPCs from the 1980s to 2000 in studies from Australia and the USA. In Tasmania, there was an increasing trend in the risk of any second cancer from 1980-2013. The competing mortality due to MPCs increased from the 1980s to a peak for first cancers diagnosed in 1995-1999. From 2006-2015, the competing mortality due to cardiovascular events increased significantly with age at first cancer diagnosis and exceeded other competing events at age 65 years or older.

Conclusions: In Tasmania, the risk of MPCs has increased with periods of first cancer diagnosis from 1980-2009. The competing mortality due to MPCs increased for first cancers diagnosed in the 1990s possibly indicating overdiagnosis of non-fatal first cancers in the 1990s. Cardiovascular events were the leading cause of competing mortality among

Abstract

Tasmanian patients diagnosed with a first cancer from 2006-2013 suggesting potential opportunities for preventive interventions.

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Publications Arising from the Thesis

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Chapter 4: Ye Y, Otahal P, Wills KE, Neil AL, Venn AJ. Temporal trends in the risk of second primary cancers among survivors of adult-onset cancers, 1980 through 2013: An Australian population-based study. *Cancer.* 2018;124(8): 1808-1818.

Chapter 5: Ye Y, Otahal P, Wills KE, Neil AL, Venn AJ. Temporal trends in competing mortality from second and subsequent primary cancers, 1980-2014: An Australian population-based study. *Cancer Epidemiology.* 2018;55: 61-67.

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October, 2018	European Society for Medical Oncology (ESMO) 2018 Congress Munich, Germany – 19 Oct - 23 Oct 2018 "Cardiovascular and other competing causes of death among cancer patients, 2006-2015: An Australian population-based study" (Poster presentation)
September, 2017	European Society for Medical Oncology (ESMO) 2017 Congress Madrid, Spain – 08 Sep - 12 Sep 2017 "Risk of second primary cancers and competing mortality in survivors of adult-onset cancer: changing pattern over three decades" (Poster presentation)
July, 2017	Haematology/Oncology/Palliative Care Meeting Royal Hobart Hospital, Australia – 18 Jul 2017 "Cause-specific mortality among cancer patients: changing patterns over three decades" (Oral presentation)
September, 2016	2016 Australasian Epidemiological Association (AEA) 23rd Annual Scientific Meeting, Canberra, Australia – 14 Sep - 16 Sep 2016 "Changing Trends in the Risk of Second Primary Cancers among Survivors of Adult-onset Cancer in Tasmania, 1980-2013: A Population-based Study" (Oral presentation)
July, 2016	Haematology/Oncology/Palliative Care Meeting Royal Hobart Hospital, Australia – 26 Jul 2016

"Increasing Trends in the Risk of Second Primary Cancers in Tasmania, 1980-2013: A Population-based Study"

(Oral presentation)

November, 2015 2015 Clinical Oncology Society of Australia (COSA) 42nd Annual Scientific Meeting, Hobart, Australia – 17 Nov - 19 Nov 2015

"Temporal Trends in the Risk of Developing Multiple Primary Cancers: A Systematic Review"

(Poster presentation)

November, 2015 2015 5th Australia-China Biomedical Research Conference (ACBRC), Hobart Satellite Meeting

Hobart, Australia – 02 Nov 2015

"Temporal Trends in the Risk of Developing Multiple Primary Cancers: A Systematic Review"

(Poster presentation)

September, 2015 Haematology/Oncology/Palliative Care Meeting

Royal Hobart Hospital, Australia – 29 Sep 2015

"Temporal Change in the Risk of Developing Multiple Primary Cancers"

(Oral presentation)

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"Temporal Trends in the Risk of Developing Multiple Primary Cancers: A Systematic Review"

(Poster presentation)

Awards Resulting from the Thesis

October, 2018	European Society for Medical Oncology (ESMO) 2018 Congress Merit Award (AUD ≈ $3000)
September, 2017	European Society for Medical Oncology (ESMO) 2017 Congress Travel Award (AUD ≈ $3000)
September, 2017	University of Tasmania Conference and Research Travel Funding (AUD ≈ $1600)
September, 2016	Australasian Epidemiology Association (AEA) Student Award (AUD = $500)
November, 2015	Best Poster Award- First place 5th Australia-China Biomedical Research Conference (ACBRC), Hobart Satellite Meeting (AUD = $250)
September, 2014	Tasmanian Graduate Research Scholarship, 2014

List of Abbreviations

ABS	Australian Bureau of Statistics
ACD	Australian Cancer Database
ACR	Australian Coordinating Registry
AER	Absolute Excess Risk
AIHW	Australian Institute of Health and Welfare
AML	Acute Myeloid Leukaemia
ASR	Age–Standardised incidence Rates
BCC	Basal Cell Carcinoma
CHR	Hazard Ratio derived from Cox model
CI	Confidence Interval
CIF	Cumulative Incidence Function
CLL	Chronic Lymphocytic Leukaemia
CML	Chronic Myeloid Leukaemia
COD-URF	Cause of Death Unit Record File
COPD	Chronic Obstructive Pulmonary Disease
CR	Competing Risk
CT	Computed Tomography
CVD	Cardiovascular Disease
HPV	Human Papillomavirus
HR	Hazard Ratio
IACR	International Association of Cancer Registries

IARC	International Agency for Research on Cancer
ICD-10	International Classification of Diseases, Version 10
ICD-O3	International Classification of Diseases for Oncology, Third Edition
IQR	Interquartile Range
KM	Kaplan-Meier
MCC	Merkel Cell Carcinoma
MM	Multiple Myeloma
MPC	Multiple Primary Cancer
NHL	Non-Hodgkin Lymphoma
NMSC	Non-melanoma Skin Cancer
PET/CT	Positron Emission Tomography - Computed Tomography
PRISMA	Preferred Reporting Items for Systematic Reviews and Meta-Analyses
PSA	Prostate Specific Antigen
PYR	Person-Years at Risk
RBDM	Registry of Births, Deaths and Marriages
RR	Relative Risk
SCC	Squamous Cell Carcinoma
SEER	Surveillance, Epidemiology, and End Results
SHR	Subdistribution Hazard Ratio
SIR	Standardised Incidence Ratio
SMR	Standardised Mortality Ratio
SPC	Second Primary Cancer (Chapter 4) Subsequent Primary Cancer (Chapters 5 and 6)

STROBE	STrengthening the Reporting of OBservational studies in Epidemiology
TCR	Tasmanian Cancer Registry
USA	United States of America

List of Tables

List of Figures

Table of Contents

Chapter 1: Introduction

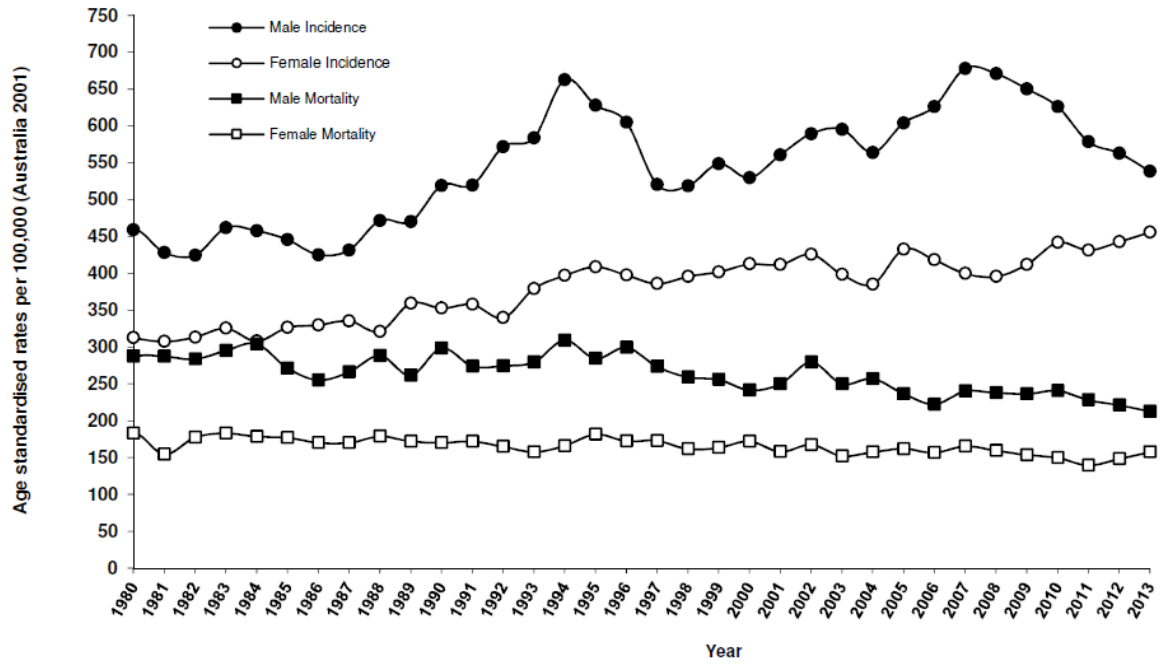
This chapter aims to provide an overall background to the studies presented in this thesis. The introduction starts with the rationale for studying multiple primary cancers and the definition of multiple primary cancers. A particular emphasis will be placed on the factors associated with temporal change in the risk of developing multiple primary cancers. Mortality from multiple primary cancers and non-cancer events among adult-onset cancer patients in the presence of competing risks will be introduced.

1.1 The rationale for studying multiple primary cancers

1.1.1 Increased cancer incidence

The number of new cancer cases has continued to increase worldwide [1]. In Australia, the age–standardised incidence rates (ASR) (standardised to the Australian 2001 population) for all cancer types (excluding non-melanoma skin cancers) increased from 472 per 100,000 for males and 328 per 100,000 for females in 1982 to 562 per 100,000 for males and 416 per 100,000 for females in 2013 [2]. Cancer incidence in Tasmania (an island state of Australia) has a similar pattern to the national statistics. The ASR (standardised to the Australian 2001 population) for all cancer types (excluding non-melanoma skin cancers) increased from 425 per 100,000 for males and 316 per 100,000 for females in 1982 to 556 per 100,000 for males and 456 per 100,000 for females in 2013 (Figure 1.1) [3]. The cancer types that contributed most to the increase in cancer incidence in Tasmania during the 31-year period were prostate cancer and malignant melanoma for males and malignant melanoma, breast cancer and lung cancer for females [3]. The aging population, advances in diagnostic techniques and sensitive screening contributed to this growing number of new cancer diagnoses [2, 4].

Figure 1.1 Trends in age standardised incidence and mortality of all cancers (excluding non-melanoma skin cancers) in Tasmania (1980-2013) (Source: Reproduced from Cancer in Tasmania: Incidence and Mortality 2013. Tasmanian Cancer Registry, 2015) [3]

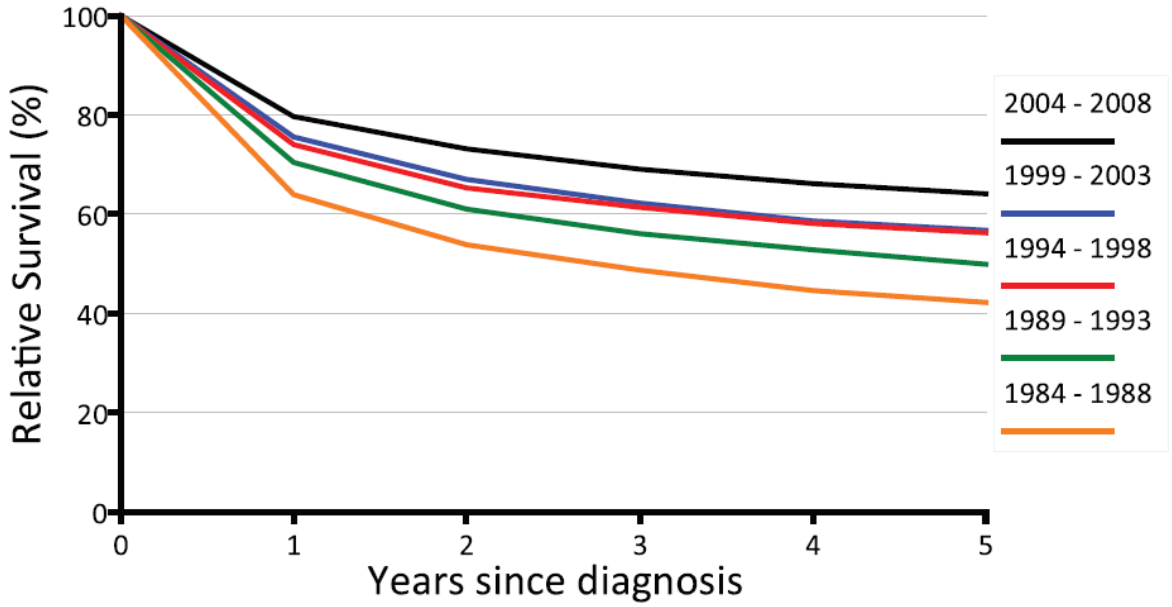


1.1.2 Improved cancer survivorship

The past 30 years have seen gradual improvements in the prognosis of individuals with various malignant cancers in most developed countries [5-7]. In Australia, the 5-year relative survival for all cancers combined (excluding non-melanoma skin cancers) rose from 48% in 1984-1988 to 68% in 2009-2013 [7]. Relative survival is a standard approach for estimating population-based cancer survival which compares the survival probability for a given amount of time after cancer diagnosis with that expected in the general population of the same age and sex and at the same time [2, 7]. In Tasmania, the 5-year relative survival for all cancers combined (excluding non-melanoma skin cancers) increased from 42% in 1984-1988 to 64% in 2004-2008 (Figure 1.2) [8]. These improvements can be attributed to advances in early diagnosis, developments in treatment techniques and regimens, optimised supportive care and

the introduction of sensitive screening for specific cancer types in Australia since the 1990s and potential overdiagnosis of cancer [2, 7, 9].

Figure 1.2 Trends in relative survival by periods of diagnosis for all cancers (excluding non-melanoma skin cancers) in Tasmania (1984-2008) (Source: Reproduced from Cancer survival and prevalence in Tasmania 1978-2008. Tasmanian Cancer Registry, 2012) [8]



Increased cancer incidence and improved cancer survival have made cancer the leading cause of disease burden in Australia since 2003 [10]. In 2012, nearly one million Australians, were living with a history of cancer since 1982 [2], 4.3% of all Australians in 2012. People with a history of cancer are growing older as they survive longer, and represent a large population potentially susceptible to the development of second or subsequent (i.e. multiple) primary cancers [11-14].

1.2 Definition of multiple primary cancers (MPCs)

1.2.1 History

In 1889, Billroth reported a patient who developed a primary gastric carcinoma after the removal of a spinocellular epithelioma of the right ear [15]. This is the first clear report of a case of MPC. This report validated that a patient could develop two independent cancers almost at the same time [16]. The criteria applied in the definition of MPCs were not established until 1932 when Warren and Gates were able to review 1,259 MPC cases from the world's literature [17]. MPCs were defined by the following criteria: (1) each tumour must present a definite picture of malignancy; (2) each tumour must be distinct; (3) the probability that one lesion is metastatic from the other must be excluded [16].

1.2.2 Current coding rules for MPCs

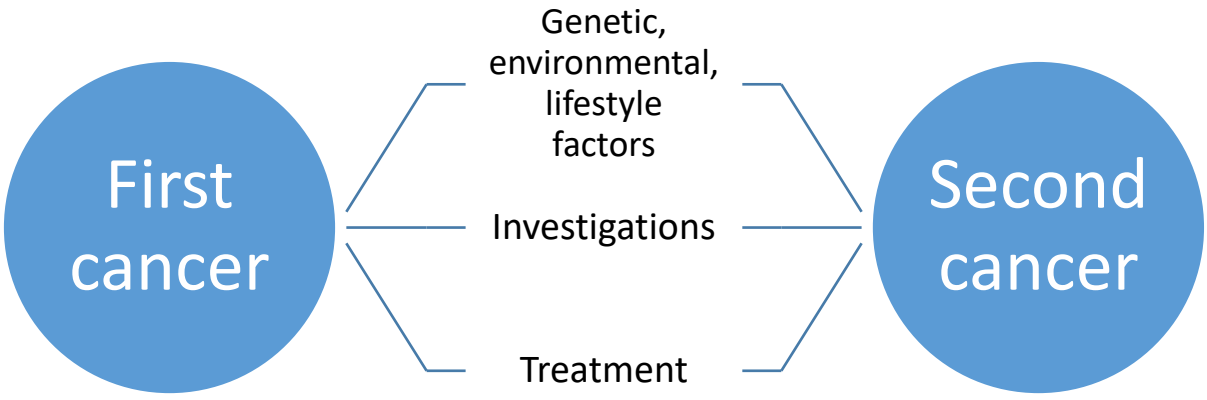
The Surveillance, Epidemiology, and End Results (SEER) Program first published MPC rules in 1975 and revised the rules in 2007 [18, 19]. SEER coding rules were applied in the United States and the majority of Canadian provinces. To make consistent comparisons across various countries and registries, the World Health Organization's International Agency for Research on Cancer (IARC) and the International Association of Cancer Registries (IACR) developed International Rules for Multiple Primary Cancers (International Classification of Diseases for Oncology, Third Edition) in 2004 [20]. IARC coding rules for MPCs were applied in most parts of the world including Australia, and have been used in this thesis. According to IARC rules, two or more primary cancers occurring in an individual that originate in a primary site or tissue and that are neither an extension, nor a recurrence, nor metastasis were classified as MPCs. IARC rules state that a person can have only one cancer per organ or pair of organs or tissue except when multiple cancers within an organ have different

morphology. In general, IACR rules are more restricted than SEER rules in allowing the registration of MPCs, particularly for cancers that occur in paired organs, at the same anatomic site and with the same histologic type. Overall, IACR rules result in fewer MPCs being registered than SEER rules [21].

1.3 Factors associated with trends in the development of MPCs

The research community has made great efforts in elucidating factors associated with the development of MPCs (Figure 1.3). In summary, first and subsequent primary cancers may share the same genetic susceptibility, environmental exposure or lifestyle factors [12]. Increased medical surveillance such as increased screening programs and the use of medical imaging technologies after the diagnosis of a first cancer may increase the possibility of detecting new primary cancers among cancer survivors. Treatment for the first cancer could also induce treatment-related MPCs as has been found for radiotherapy, chemotherapy and/or hormonal therapy [22-24].

Figure 1.3 Factors associated with ascertainment of multiple primary cancers



For most MPC patients, it is likely that a combination of several risk factors result in the development of their MPCs [12, 23]. For genetic factors, to the best of our knowledge, only when

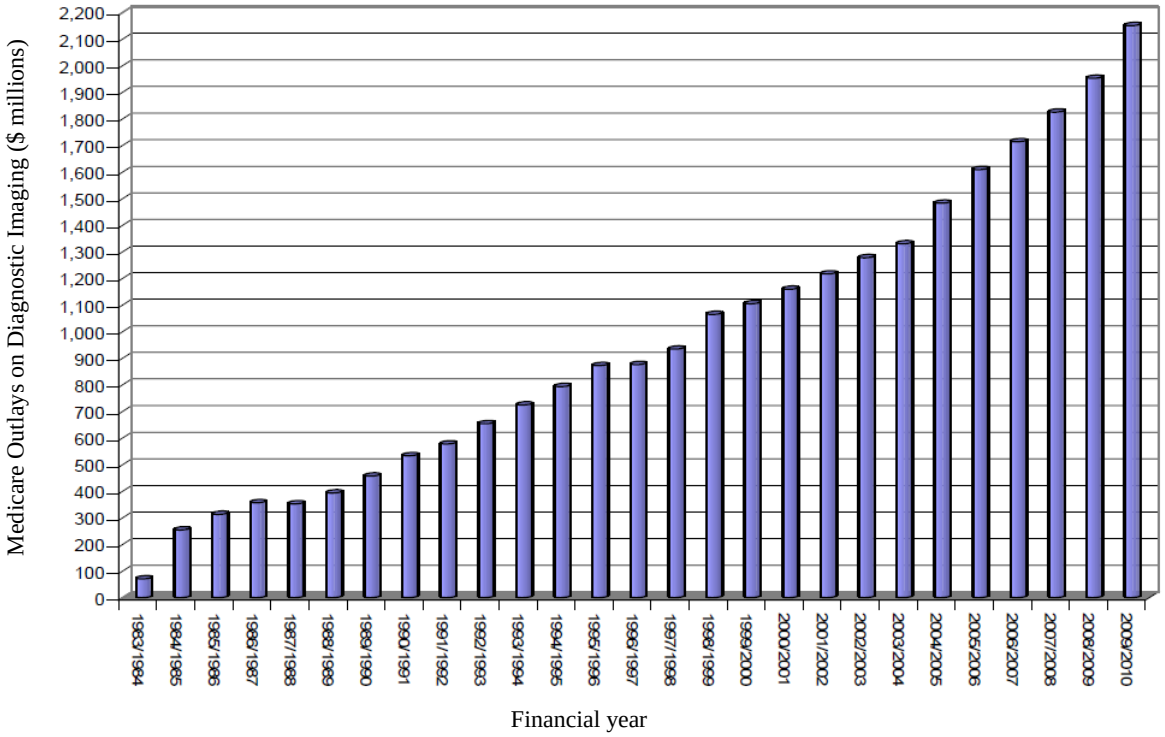
there is an interaction with another factor (e.g. a gene – environment interaction) may temporal trends in the development of MPCs arise [12, 22-23]. Therefore, factors associated with trends in the development of MPCs are described by changes in medical investigations, treatment regimens for cancer and lifestyle, environmental factors in the next section.

1.3.1 Medical investigations

1.3.1.1 Medical imaging

The use of medical imaging procedures has increased dramatically worldwide since the 1980s [25]. In the United States, the number of radiologic and nuclear medicine procedures has increased about 10-fold and 2.5-fold respectively from 1980 to 2006 [25, 26]. In Australia, the outlays for diagnostic imaging provided by the government rose from $255 million in 1984/85 to $2,150 million in 2009/10 (Figure 1.4) [27]. Diagnostic radiology contributed most to the cost of diagnostic imaging services in recent years. Cancer survivors usually receive more frequent radiologic imaging than the general population due to post-treatment surveillance [28-30]. More frequent radiologic imaging tests is also associated with a higher probability of incidental findings. A systematic review of 44 articles published until December 2007 identified a mean frequency of 31.1% incidental findings from computed tomography (CT) scans [31]. Cancers ascertained from incidental findings are sometimes referred to as ‘incidentalomas’ and may be of minor clinical significance [32]. Therefore, cancer survivors may have a higher chance of being detected with a new cancer than the general population due to more frequent medical imaging [33].

Figure 1.4 Annual Medicare (Australia's publicly funded universal health care system) outlays on diagnostic imaging in Australia ($ millions) (Source: Reproduced from Review of Funding for Diagnostic Imaging Services: Final Report. Medical Benefits Reviews Task Group, Diagnostic Imaging Review Team, Department of Health and Ageing, Australia 2011) [26]



The growing application of radiologic imaging such as CT scanning could also be a source of increased radiation exposure to cancer survivors. The association between ionizing radiation exposure and cancer risk was well documented in studies of cancer incidence among Japanese atomic bomb survivors [34, 35]. Since the introduction of CT scanning in the 1970s, the application of medical imaging procedures has become the largest man-made source of ionizing radiation [26, 36]. Evidence from epidemiological studies has linked the risk of cancer with common diagnostic imaging procedures such as CT examinations [37-43]. This evidence includes two large retrospective studies which quantified "lifetime attributable risk" (LAR) subsequent to cardiac CT scanning. The LAR is defined as additional cancer risk above and beyond baseline cancer risk [38, 41]. LAR was found to vary from 1 in 143 for women at age 20

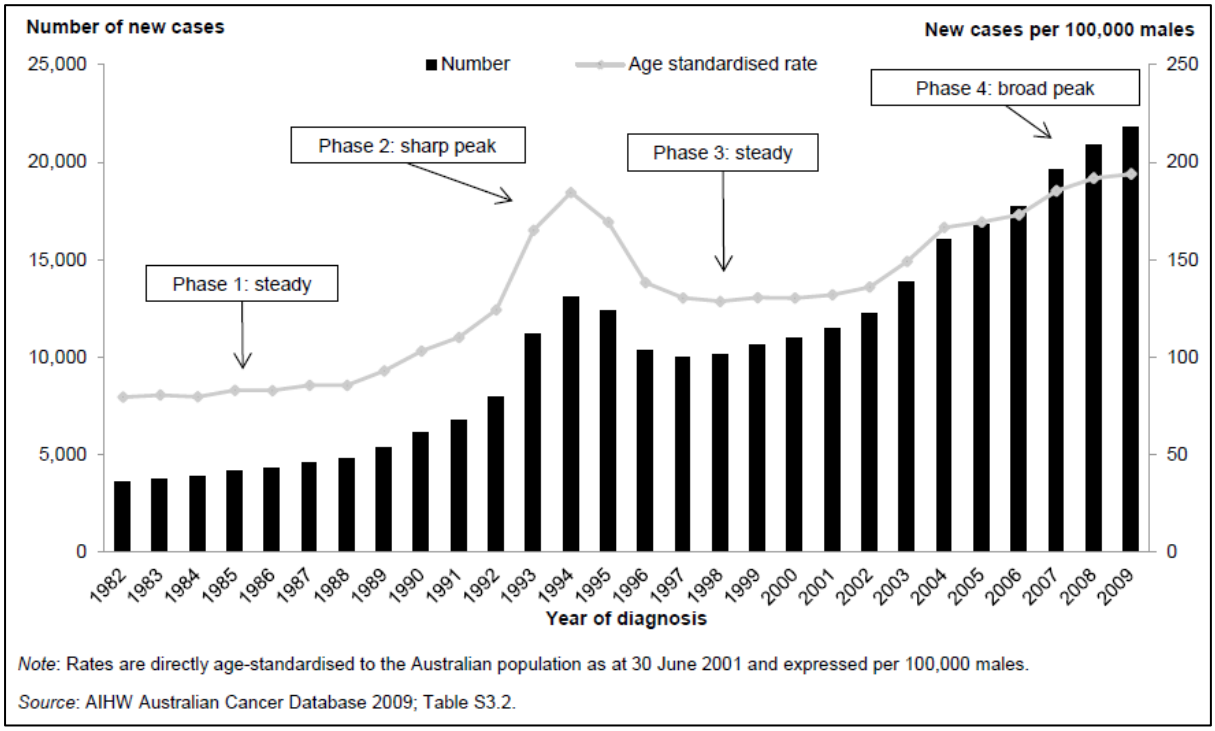
years to 1 in 270 for women at age 40 years, and 1 in 600 for men at age 40 years to 1 in 3261 for men at age 80 years [38, 41]. In addition, a large cohort study of over 31,000 patients who underwent 190,712 CT scans over 22 years found that the increased cumulative CT radiation exposure due to recurrent CT scans increased baseline cancer risk [44]. As cancer survivors usually undergo frequent CT imaging during follow-up, their risk of developing MPCs may also increase as a consequence [45].

1.3.1.2 Cancer screening

Cancer screening programs were established in most developed countries around the 1990s, although non-programmatic screening would have been available earlier. In the United States, the application of cancer screening for cervical cancer, breast cancer, colorectal cancer and prostate cancer has increased since 1987 [46, 47]. In the European Union, screening practice for cancer varied across countries and the starting time ranged from the 1970s for Finland to the 2000s, with most commencing in the 1980s [48, 49]. In Australia, national cancer screening programs for breast and cervical cancer were implemented in 1991 and bowel cancer screening started in 2006 [2]. Non-programmatic screening for prostate cancer through prostate specific antigen (PSA) testing began to be subsidised by Medicare (Australia's publicly funded universal health care system) in 1989. This was associated with a sharp increase of prostate cancer incidence in the early 1990s (Figure 1.5), with an overall 144% increase in prostate cancer incidence between 1982 to 2009 [50] .

A meta-analysis of 20 studies published until 2010 found that cancer survivors undertook 27% more frequent cancer screening tests for breast, cervical, colorectal and prostate cancers than individuals without cancer [51]. Therefore, the chance of detecting MPCs may be higher since the 1990s, the screening era, than previously.

Figure 1.5 Prostate cancer incidence among males in Australia 1982-2009 (ASR was standardised to the Australian 2001 population) (Source: Reproduced from Prostate cancer in Australia. Australian Institute of Health and Welfare 2013) [52]



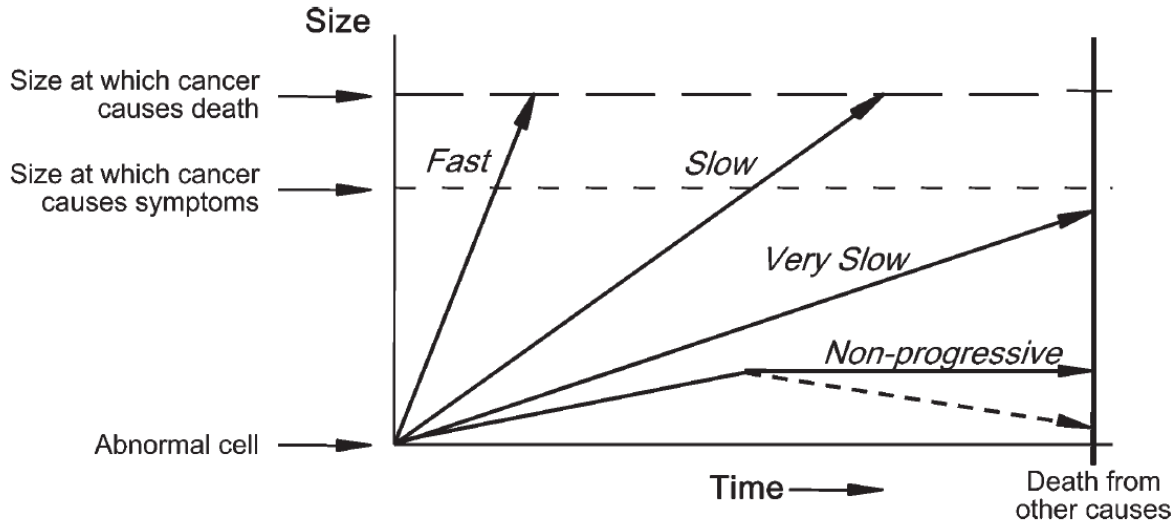
1.3.1.3 Overdiagnosis in cancer

Increased medical investigation contributes to the increased ascertainment of new primary cancers and cancer survivors generally experience more radiologic imaging and/or screening procedures than the general population [28-30, 51]. However, despite benefits from early detection of cancer, increased application of imaging techniques or screening for specific cancer types presents potential adverse effects through the detection of more 'indolent cancers'. 'Indolent cancers' are cancers that achieve the pathological criteria for cancer but do not cause symptoms or death. Diagnosis of these cancers is considered as overdiagnosis [32].

Welch and Black described four types of cancer progression as illustrated in Figure 1.6 [32]. The arrows labelled 'Fast' and 'Slow' represent fast-growing and slow-growing cancers. Cancers of these two types will cause symptoms or death before the person dies of other

causes. The arrows labelled 'Very Slow' and 'Non-progressive' represent cancers that grow very slowly or never progress during the person's lifetime respectively. These cancers will not cause symptoms or death before the patient dies of other causes. Overdiagnosis usually occurs through the detection of 'Very slow' and 'Non-progressive' cancer types.

Figure 1.6 Four types of cancer progression (Source: Reproduced from Overdiagnosis in cancer. Journal of the National Cancer Institute 2010) [32]



Screening for breast cancer and increased use of PSA testing appears to identify cancer types that were potentially overdiagnosed in Australia, as well as in other developed countries [50, 52-55]. Screening for lung cancer may also follow this pattern [56, 57]. A recent meta-analysis combining 20 studies observed 27% more frequent screening practices among cancer survivors than in the general population [51]. In addition, a Korean study of 512 cancer survivors found that these cancer survivors proactively pursued screening for potential MPCs if their first cancers were screen-detected [58]. As a result, overdiagnosis may more likely occur in cancer survivors than the general population.

1.3.2 Cancer treatment

Innovation in the development of therapeutic drugs for cancer and progress in combined cancer therapy regimens have successfully prolonged the survival time after first cancer diagnosis [59-61]. However, the potential risk of developing treatment-related MPCs has raised concerns in relation to the use of aggressive treatment regimens [24]. Numerous studies have illustrated and quantified the risk of treatment-related cancers following radiotherapy or chemotherapy [62-68].

The awareness of the risk of MPCs following radiotherapy came from the association between ionizing radiation and cancer risks [69, 70]. Different organs have different susceptibility to radiation. Solid cancers that are easily induced by radiotherapy include second cancers of lung cancer, female breast cancer, head and neck cancer and male oesophageal cancers [64, 71-73]. Haematological malignancies such as acute myeloid leukaemia (AML) could also be triggered by radiotherapy for cancer [66, 68, 74].

For radiotherapy-related MPCs, two meta-analyses reported a 22% higher risk of MPCs following radiotherapy for breast cancer and 67%-79% higher risk of MPCs following radiotherapy for prostate cancer [75, 76]. A large cohort study of 647,672 cancer patients collected from the United States cancer registries reported that the relative risks for radiotherapy-related MPCs ranged from 1.08 (95%CI 0.79-1.46) following first cancer of the eye and orbit to 1.43 (95%CI 1.13-1.84) following testicular cancer [63].

Innovations in radiotherapy techniques have changed clinical practice and advanced imaging helps to target tumour issues more accurately [77, 78]. However, some modern techniques such as intensity-modulated radiation therapy may enhance the risk of radiation-induced second cancers and the risks vary with technique used [78-82]. It is worthy of note that although the risk

of MPCs increases after radiotherapy for cancer, the proportion of second cancers that could be attributable to radiotherapy in adults appears to be relatively small [63]. The large United States cohort study of 647,672 cancer patients estimated that for all MPCs developed in patients with radiotherapy, only 8% of them could be considered as radiotherapy-related [63].

Some chemotherapy drugs such as alkylating agents could induce chemotherapy-related AML [23, 67, 83]. As chemotherapy regimens evolved during the past decades, the risk of MPCs that could be attributable to chemotherapy may have changed over time. Evidence from a large-scale cohort study of 426,068 patients who initially received chemotherapy showed various trends in the risk of chemotherapy-related AML over time, and the trends were generally consistent with changes in treatment regimens for different cancer types [62]. It is also noted that the occurrence of chemotherapy-related MPCs is rare and data from this study reported only 801 chemotherapy-related AML cases among 426,068 patients (less than 0.2%).

1.3.3 Lifestyle or environmental factors

First and subsequent primary cancers may share the same environmental or lifestyle factors. The association between the development of MPCs and smoking or alcohol intake have been well documented [84-91]. The prevalence of smoking in Australian adults has continued to decrease from 1980 to 2013 [92]. Alcohol consumption in the general Australian population has presented a decreasing trend since 1991 also [93]. Changing trends in cigarette smoking and alcohol intake may result in corresponding changes in the risk of smoking-related MPCs and alcohol-related MPCs over time [89, 90, 94].

A shift in the pattern of oncogenic environmental factors may also contribute to temporal changes in the risk of developing MPCs. For example, the aetiology of head and neck cancer

has altered from being primarily smoking and alcohol-associated to primarily Human Papillomavirus (HPV)-associated in the United States and in European countries during the past two decades [95-97]. Temporal trends in the risk of developing smoking and alcohol-related MPCs and HPV-related MPCs may be impacted as a result [94, 98].

As the factors associated with MPC development have changed over time, whether the risk of MPCs has also changed as a consequence remains unknown. A systematic review of temporal trends in the risk of developing MPCs worldwide will be presented in Chapter 3. Temporal trends in the risk of second primary cancers among Tasmanian cancer patients during 1980-2013 will be described in Chapter 4.

1.4 Mortality from MPCs and the presence of competing risks

For patients with MPCs, the occurrence of MPCs will compete with their first cancer and potential non-cancer events (e.g. cardiovascular events) as the primary cause of death. Traditional methods such as Kaplan-Meier (KM) survival analysis and Cox regression models consider the time from the diagnosis of first cancer to the primary outcome of interest. These methods have been appropriately applied in estimating overall survival and all-cause mortality for patients with MPCs [99-103]. However, they usually overestimate the mortality risk due to a specific cause (e.g. death due to a MPC) because they fail to account for the presence of competing risks [104-110]. Competing risk settings are present when the occurrence of an event (e.g. death due to a cardiovascular event) precludes the occurrence of the primary outcome (death due to MPC) [106]. For KM analyses, when a specific cause of death is the primary outcome of interest, patients who died of other causes were considered as ‘censored’ events. The KM method assumes that ‘censored’ patients have the same prognosis as patients who are still alive at the end of the study. Obviously, this assumption is not valid

because patients who died of other causes have a probability of zero to reach the primary outcome of interest. In competing risk settings, patients who experience a competing event (e.g. die of a cardiovascular event) are not censored and will not reach the primary outcome of interest anymore. Competing risk approach estimates "real world" probabilities of cause-specific deaths. A more detailed illustration of the difference between KM settings and competing risk settings will be described in Chapter 2.

Despite these benefits, competing risk analyses have not been frequently used by researchers. This may be due to limitations of the major statistical software, in that they may require several days to run the competing risk models in Stata for a large cohort study [111]. In 2016, *Circulation* and *Journal of the National Cancer Institute* published statistical tutorials to introduce competing risk models for survival analyses [106, 112]. The competing risk models run more efficiently using the R package 'cmprsk' released in February 2015 [113]. A recent study has applied competing risk analysis to estimate cause-specific mortality among individuals with diabetes [114]. However, studies of MPC mortality among cancer patients in the presence of competing risks are limited. The first population-based study describing temporal trends in MPC mortality since 1980 among adult-onset cancer patients considering the presence of competing risks will be presented in Chapter 5 of the thesis.

1.5 Non-cancer events as a competing cause of death

An important competing cause of death among cancer patients is death from a non-cancer event. Some cancer treatments may increase the chance of developing treatment-related non-cancer events such as radiation-associated or chemotherapy-related cardiovascular events [115, 116]. Cancer survivors may also experience multiple chronic diseases with aging and longer survival. Evidence from Sweden and the United States has shown that, over time, patients

with prostate cancer have become less likely to die from their primary cancer and more likely to die from non-cancer events (e.g. death due to cardiovascular events) [117]. This study analysed cause of death among 210,112 men diagnosed with prostate cancer registered in the national Swedish Cancer Registry during 1961-2008 and 490,341 men diagnosed with prostate cancer registered in the United States registries during 1973-2008. Increased mortality due to non-cancer events has also been found for advanced cancer types other than prostate cancer. For example, non-cancer events were the leading cause of competing mortality among Korean patients with advanced head and neck cancer treated at one tertiary referral hospital between 2001-2010 [118]. Of the non-cancer events, increased risk of cardiovascular death among cancer patients has led to growing concern in the clinical and research communities [119-121]. In part this is due to some life-threatening cardiovascular events being induced by cancer treatment such as chest radiation or conventional chemotherapeutic drugs (e.g. cytotoxic agents and anthracyclines) [122, 123]. Cancer diagnosis and treatment may also aggravate underlying cardiovascular disease among cancer patients [124]. In this era of personalized cancer therapy, better understanding of how non-cancer events, especially how cardiovascular events contribute to death among cancer patients is important to the stratification of individualized treatments.

1.6 Summary

The use of medical imaging and cancer screening tests has increased worldwide during recent decades. Cancer patients tend to receive more frequent investigations than the general population due to follow-up care after primary diagnosis. Treatment protocols and therapeutic agents for cancer have evolved and some environmental and lifestyle factors associated with cancer development have changed over the past decades. The risk of MPCs may have changed over time due to these changing factors. Therefore, a systematic review was

undertaken to determine if there has been a temporal change in the risk of developing MPCs worldwide. Based on findings from the systematic review, we used original data from the Tasmanian Cancer Registry (TCR), a population-based registry covering the entire state of Tasmania, Australia, to explore temporal trends in the risk of second primary cancers among Tasmanian cancer patients during 1980-2013.

The aging population, successful treatment of first cancers and advanced imaging increase the chance of detecting MPCs. The numbers of patients with MPCs may increase consequently. Cancer patients may also experience devastating non-cancer events related to their cancer treatment (e.g. chemotherapy–related cardiac dysfunction) or as a result of a deterioration of pre-existing non-cancer disease. The occurrence of MPCs and non-cancer events compete with the first cancer as the cause of death among cancer patients. Traditional studies frequently used Kaplan-Meier analysis and Cox regression models for cause-specific mortality analysis which failed to consider the presence of competing risks. We performed competing risk analysis to assess the competing mortality from MPCs and non-cancer events among Tasmanian cancer patients. The detailed research aims are outlined below.

1.7 Research aims

1. To conduct a systematic review of the scientific literature to determine whether the risk of MPCs has increased over recent decades (Chapter 3).
2. To investigate trends in the risk of second primary cancer among adult cancer survivors in Tasmania during 1980-2013 (Chapter 4).
3. To assess subsequent primary cancer mortality among Tasmanian adult-onset cancer patients in competing risk models and to investigate their patterns since 1980 (Chapter 5).

4. To assess the risk of non-cancer deaths among Tasmanian cancer patients in competing risk models during 2006-2015 (Chapter 6).

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Chapter 2: Methods

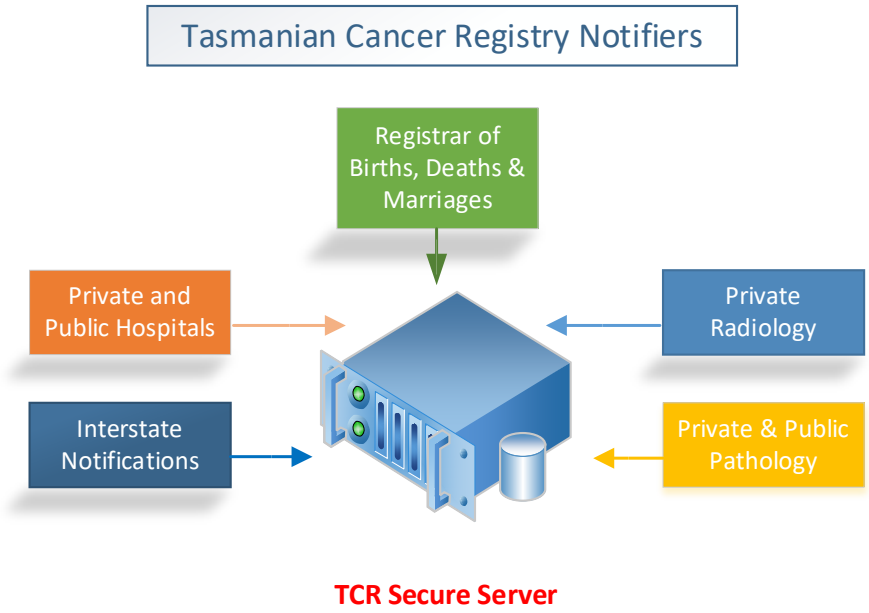
Except for the systematic review presented in Chapter 3, Chapters 4, 5 and 6 conducted analyses using data from the Tasmanian Cancer Registry (TCR). This Methods chapter provides an overview of the data handling, collection and coding practices used by the TCR and linked cause of death information held in the Cause of Death Unit Record File (COD-URF). Descriptions of statistical analyses performed for each study are presented in the corresponding chapters. This section presents additional details relevant to the statistical analyses.

2.1 Data sources

2.1.1 Tasmanian Cancer Registry (TCR)

The TCR was established in 1977 as a population-based registry covering all of Tasmania, an island state of Australia. The TCR is responsible for collecting and collating all malignant neoplasms in Tasmanian residents, reporting accurate cancer incidence and mortality statistics to the State Government and for reporting cancer incidence and mortality trends. The TCR also contributes data to the Australian Cancer Database (ACD) on an annual basis in support of national cancer reporting. The ACD is managed by the Australian Institute of Health and Welfare. Cancer was declared a notifiable disease in Tasmania in December 1992, and has had a legislative basis since this time. TCR records are not considered to be complete for the years 1977-1979 during the establishment of the Registry, therefore these years were excluded from analyses in this thesis. Cancer incidence remained stable after cancer was declared a notifiable disease suggesting there was already high ascertainment prior to 1992. All pathology laboratories in Tasmania, both public and private, provide the TCR with copies of histopathological and cytology reports of cancer and cell marker reports in electronic form

on no less than a weekly basis. Private and public hospitals in Tasmania provide the TCR with International Classification of Diseases, Version 10 (ICD-10) coded episodes in electronic form for inpatients treated for cancer on either a monthly or an annual basis. Paper-based reports are received where there is no capacity to obtain electronic notifications of cancer, and are typically received from interstate hospitals, other Australian cancer registries and pathology laboratories on an ad-hoc basis. (See figure below).



Non-melanoma Skin Cancers (NMSCs) are non-reportable by law in Tasmania, but are received electronically by the TCR on a regular basis. They are not routinely registered due to funding limitations and are excluded in the data reported within this thesis. The topography (primary site) and morphology of cancer cases were coded by TCR clinical coders according to International Classification of Disease for Oncology, Third Edition (ICD-O3). Ascertainment of MPCs followed the International Rules for Multiple Primary Cancers (ICD-O Third Edition) proposed by the International Association of Cancer Registries (IACR) and the International Agency for Research on Cancer (IARC).

All deaths in Tasmania, for which a coronial inquiry is not required, must be certified as to cause and date of death by a registered medical practitioner with the certificate in turn registered by the Registry of Births, Deaths and Marriages (RBDM). Details of all registered deaths in Tasmania are forwarded to the Australian Bureau of Statistics (ABS) by the RBDM Tasmania, who in turn check and code each death according to ICD-10. The TCR similarly receives registrations of all deaths in the population from the RBDM monthly in electronic format and code cancer related deaths in ICD-O3 using the TCR cause of death coding guidelines. Each death recorded in the TCR dataset included up to five causes of death, up to eight antecedent causes of death and up to two other significant conditions noted at time of death. Deaths coded to ICD-O3 are subsequently converted to ICD-10; causes of deaths that were considered not related to cancer were coded using a uniform code of '9999'.

2.1.2 Cause of Death Unit Record File (COD-URF)

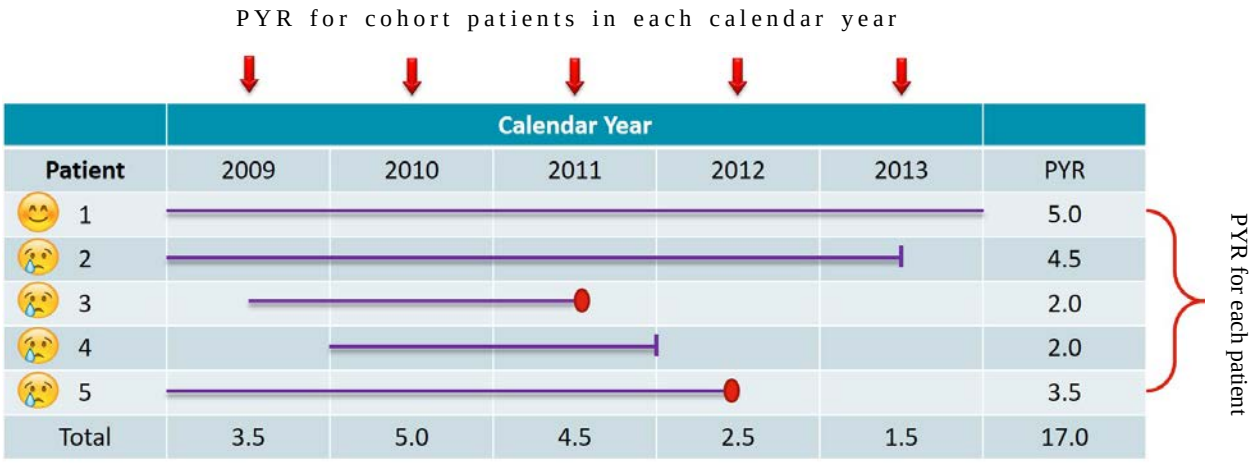
The Cause of Death Unit Record File (COD-URF) is a dataset covering all deaths and the causes of deaths registered in Australia since 2006. It is managed by the Australian Coordinating Registry (ACR), who receive this data from the ABS. Under a contractual agreement, the ACR provides the COD-URF to the Tasmanian Data Linkage Unit. TCR records of deceased individuals with a first cancer registered during 2006-2013, and followed up to December 2015, were linked by the TDLU with the nationally coded COD-URF for Tasmania. Through the process of data linkage with the nationally coded COD-URF, we are able to gain a better understanding of competing mortality from specific non-cancer events among cancer patients. Where variations were identified in the TCR coded cause of death, and that recorded in the COD-URF, individual medical records were accessed to obtain further information to more accurately identify if death was cancer related.

2.2 MPC incidence risk

2.2.1 Person-years at risk (PYR)

We used a standard person-years approach to conduct the analysis [1, 2]. Person-years at risk (PYR) started 2 months after a first cancer diagnosis and ended at the date of the second cancer diagnosis, the date of death, or the end of follow-up, whichever came first. Most cancer registries use a 2-month rule to define the development of a MPC because for MPCs occurring within 2 months, it is difficult to determine which one was the first cancer. Below is an example of the calculation of PYR in our study cohort (Figure 2.1).

Figure 2.1: Example illustrating the calculation of person-years at risk (PYR)



The first patient had a first cancer diagnosis in late 2008 and PYR started at the beginning of 2009 (2 months after a first cancer diagnosis). The first patient was still alive at the end of 2013. The PYR for the first patient is 5 years. The PYR for the second patient started at the beginning of 2009 and the patient died in the middle of 2013 and had PYR for 4.5 years. The PYR for the third patient started in the middle of 2009 and the patient developed a second primary cancer in the middle of 2011. The PYR for the third patient is 2.0 years. Similar calculations were applied for the fourth and fifth patients. Therefore, we had the PYR for

each patient at each row. If we look at the column, the PYR could also be accumulated within 1-year calendar period strata. Then we could sum the PYR within specific sex, 5-year age group and 1-year calendar period strata.

2.2.2 Outcome measures

2.2.2.1 Standardised incidence ratio (SIR)

The standardised incidence ratio (SIR) is a relative measure and was calculated as the ratio of observed to expected numbers of MPCs [2-4]. The estimation of expected numbers of MPCs assume that patients with a first cancer experienced the same cancer rates as the general population. The expected number was then calculated using the accumulated person-years within specific sex, 5-year age group and 1-year calendar period strata, multiplied by the corresponding cancer incidence rates in the general population. The SIR is more informative than the crude incidence of MPC because it takes into account the natural increase of cancer risk with age and variation of the background cancer incidence in each year [5]. In comparison, crude incidence of MPCs simply reflects the number of MPC cases occurring in the study cohort during a year. Poisson regression models were used to derive 95% confidence intervals (95% CIs) for SIRs, assuming that the observed number followed a Poisson distribution. The outcome measure used for the model was the observed number of MPCs and offset/exposure variable was the expected number of MPCs. Tests for linear trends in SIRs were performed by entering calendar periods of first cancer diagnosis as a consecutive non-negative integer variable in relevant Poisson regression models. Evidence for a linear trend was assessed by comparing the likelihood function of the model including the variable for calendar periods of first cancer diagnosis with the likelihood function of the model without that variable.

2.2.2.2 Absolute excess risk (AER)

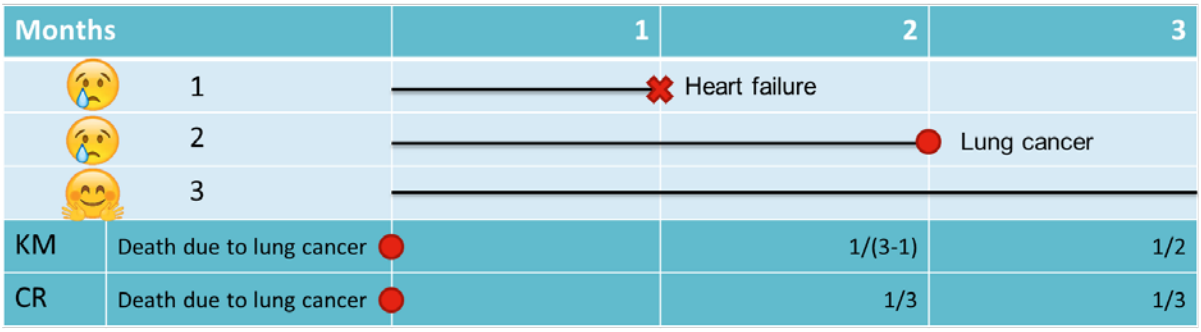
The absolute excess risk (AER) is an absolute measure. We subtracted the expected number of MPCs from the observed number of MPCs; the difference was then divided by 10,000 person-years. The AER is often interpreted as the absolute number of excess second cancers per 10,000 PYR among cancer survivors. Generally, the AER is more informative for public health purposes because it measures the absolute impact of the MPC burden among cancer patients. High SIRs may occasionally produce low AERs when the cancer incidence in the general population is low. For example, when the baseline leukaemia incidence in the general adulthood population is low, the AER for treatment-related leukaemia among adult cancer patients may have a low value. However, the relevant SIR value may be high because of the small value of the denominator (the expected number of treatment-related leukaemia using leukaemia incidence in the general adulthood population is low). In contrast, when the relevant cancer incidence in the general population is high, a slight increase in SIRs may produce a great increase in the AERs.

2.3 MPC mortality risk

2.3.1 Competing risk analysis

We applied competing risk models as an alternative to Kaplan-Meier methods to assess the competing mortality from subsequent primary cancers and non-cancer events among cancer patients. Here is a simple example to illustrate the overestimation of cause-specific mortality using the Kaplan-Meier method and the more accurate estimation using competing risk analysis [6]. Three patients were diagnosed with lung cancer at the same time. The first patient died one month after lung cancer diagnosis and the cause of death was heart failure. The second patient died two months after lung cancer diagnosis because of the progression of the

lung cancer. The third was still alive at the end of follow-up. The primary outcome of interest is the death due to lung cancer. In Kaplan-Meier (KM) estimates, the patient who died of heart failure is censored in the risk setting (the denominator) at one month. Therefore, the chance of death due to lung cancer at the third month is 1/2 in this group of three patients. In a competing risk (CR) setting, the patient who died of heart failure is still kept in the risk set (the denominator), but the chance of reaching the endpoint of interest (death due to lung cancer) is zero. As a result, the chance of death due to lung cancer at the third month is 1/3.



2.3.2 Outcome measures

As an absolute measure, the cumulative incidence function (CIF) was used to estimate the cumulative incidence of cause-specific deaths in the presence of competing risks [6, 7]. For a relative measure, the subdistribution hazard ratios (SHRs) of cause-specific deaths were calculated in competing risk models [8]. We also derived hazard ratios from Cox regression models and made comparisons with the SHRs to illustrate the difference in results in the presence of competing risks. Detailed descriptions of the analyses are presented in Chapter 5.

2.4 Non-cancer mortality among cancer patients

We conducted competing risk analysis to assess the cumulative incidence of non-cancer deaths among cancer patients. Standardised mortality ratios (SMRs) and absolute excess risks

(AERs) for non-cancer deaths were used to compare mortality due to non-cancer events among cancer patients with that expected in the general population. The rationale and calculation of SMRs were similar to that for SIRs.

2.5 Statistical analysis

Detailed descriptions of all statistical analyses performed are presented in the relevant chapters. Statistical analyses presented in Chapter 4 were performed using Stata software (StataCorp. 2011. Stata Statistical Software: Release 12. College Station, TX: StataCorp LP). Statistical analyses presented in Chapter 5 were performed in R version 3.3.2 (R Project for Statistical Computing, http://www.r-project.org) using the 'cmprsk' [9] and 'survival' [10] packages. Statistical analyses presented in Chapter 6 were performed in R version 3.4.2 (R Project for Statistical Computing, http://www.r-project.org) using the 'cmprsk' [9] and 'survival' [10] packages, and Stata software (StataCorp. 2017. Stata Statistical Software: Release 15. College Station, TX: StataCorp LLC). A two-sided P value less than 0.05 was considered statistically significant.

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Chapter 3: Temporal trends in the risk of developing multiple primary cancers: A systematic review

3.1 Abstract

Background: Cancer survivors are at risk of developing second and subsequent primary cancers, referred to as multiple primary cancers (MPCs). It is not clear whether the risk of MPCs has increased over recent decades, but increasing use of radiological imaging and potentially harmful effects of certain cancer treatments raise this possibility. A systematic review was undertaken to assess whether there has been a temporal change in the risk of developing MPCs.

Methods: A systematic search to identify population-based studies of MPCs was performed in Medline/PubMed and Embase databases from inception to August 2016. Included studies were those reporting risk of MPCs for all sites combined following a first cancer at any site or a specific site, using standard incidence ratios (SIRs) or equivalent, and with analysis stratified by calendar years.

Results: We identified 28 articles eligible for inclusion, comprising 26 population-based studies and two monographs. MPC incidence was reported in nearly 6.5 million cancer survivors. For all first cancer sites combined, a higher rate of MPCs was reported in more recent than earlier calendar periods in four of the six relevant studies. The SIRs ranged from 1.14 for a first cancer diagnosis in the early 1980s to 1.21-1.46 in the late 1990s in the USA and Australia. Two studies from Italy and France showed no significant difference in SIRs across time periods 1978-2010 and 1989-2004. The remaining 22 studies reported various

temporal trends in the risk of developing MPCs after a first cancer at a specific site, but most showed little change.

Conclusion: Overall, the risk of developing MPCs appears to have increased since the 1980s when considering studies of all primary cancer sites combined from the USA and Australia but not from Europe. With the introduction of more routine nuclear medical imaging over the last 15 years, more studies are needed to confirm recent trends of MPC risk in adult cancer survivors.

3.2 Introduction

Survival for most cancers has increased steadily over the last three decades, mainly due to increased detection of early-stage cancers and advances in cancer treatment [1, 2]. This has been a global phenomenon and has led to a growing number of cancer survivors worldwide [3, 4]. Increasing attention has been given to the long-term outcomes of cancer survivors including the risk of developing new primary cancers [5, 6]. In a seminal report from the USA, up to 10% of cancer survivors were diagnosed with a second or higher-order primary cancers during a 27-year period 1973 to 2000 [7]. A higher rate of new cancers was observed among cancer survivors with a first cancer diagnosed in more recent (between 1995 and 2000) than in earlier time periods (1973-79).

Two or more primary cancers occurring in the same individual that are neither extensions, recurrences nor metastases of each other are defined as Multiple Primary Cancers (MPCs) [8]. Factors associated with any change in the risk of developing MPCs might include increased use of diagnostic imaging and adverse cancer treatment effects. The past 30 years has seen a large increase in the use of diagnostic imaging, particularly radiologic medicine examinations such as diagnostic X-rays and computed tomography (CT) scanning [9-11]. Medical radiation exposure to the USA population has increased approximately 600% since the 1980s [12]. In addition, cancer survivors tend to receive more frequent radiologic imaging than the general population due to follow-up care after primary treatment [13-15]. The rising use of various imaging modalities might be expected, therefore, to increase the possibility of incidental findings of new cancers during a routine follow-up examination and/or may increase the future risk of cancer due to the radiation exposure [16].

Some MPCs may also be treatment-related [17, 18]. Patients treated with radiotherapy and some specific chemotherapeutics can experience a number of significant late effects. One of the most serious potential long-term side effects is the development of MPCs [19-21]. The risk of developing MPCs is increased among survivors treated with radiotherapy, alkylating agents, anthracyclines and epipodophyllotoxins [3, 21-23]. A mutation in a susceptibility gene may also promote two or more cancers in an individual [22, 24, 25]. However, genetic risk factors for MPCs would not be expected to change over recent decades, unless they interact with other risk factors that demonstrate temporal trends.

In order to better understand temporal trends in the risk of developing MPCs, we performed a systematic review of the scientific literature to determine whether the risk of MPCs has increased over recent decades.

3.3 Methods

3.3.1 Scope of the review

We conducted a systematic literature search to identify studies describing adult cancer survivors with the diagnosis of MPCs. The review was focused on the following question: has there been an increase in the risk of developing MPCs over time?

3.3.2 Search strategy and selection criteria

We used two approaches to conduct the systematic search in two phases (Table 3.1). The original review was conducted in PubMed and Embase databases for eligible articles published prior to 1st March 2015. The update was conducted to August 2016. The MeSH terms related to “multiple primary cancers” and “second cancers” and related subcategories

were used in separate searches: Neoplasms/ Multiple Primary, Neoplasms/ Second Primary and epidemiology/ prevention and control. A number of key words ("multiple primary cancer* or malignanc* or tumo*", "population-based" and "time period* or interval* or calendar years") were also used and combined in different databases.

Following the Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA) statement [26, 27], eligibility criteria for included studies were as follows: (i) Type of studies: published population-based studies and reports published in English; (ii) Types of patients: adult cancer survivors (≥19 years) who were diagnosed with a first primary cancer (index cancer); (iii) Types of outcomes measures: adult cancer survivors (≥19 years) who developed a second or higher-order primary cancer (all sites combined). Studies of cancer survivors who developed MPCs at a specific site and studies based on autopsy cases were excluded because we were interested in the overall MPC risk among adult cancer survivors. Studies of MPCs in patients undergoing specific therapies or by treatment periods were also excluded given we were interested in all factors that affected the trends in MPC risk rather than treatment effects only.

Table 3.1: Search strategy for Medline and Embase (1 March 2015)

Approach 1	
Search strategy using MeSH terms in Medline	
No.	Search
1	"Neoplasms, Multiple Primary/epidemiology"[Mesh] OR "Neoplasms, Multiple Primary/prevention and control"[Mesh] OR "Neoplasms, Second Primary/epidemiology"[Mesh] OR "Neoplasms, Second Primary/prevention and control"[Mesh] AND "Time Factors"[Mesh] N = 657
2	Limits: adults N = 498
Search strategy using keywords in Medline	
1	multiple primary cancer*[Title/Abstract] N = 576
2	multiple primary malignanc*[Title/Abstract] N = 208
3	multiple primary tumo*[Title/Abstract] N = 386
4	multiple primary carcinoma*[Title/Abstract] N = 130
5	second cancer*[Title/Abstract] N = 1,272
6	second malignanc*[Title/Abstract] N = 1,622
7	second tumo*[Title/Abstract] N = 951
8	second carcinoma*[Title/Abstract] N = 82
9	#1 OR #2 OR #3 OR #4 OR #5 OR #6 OR #7 OR #8 N = 4,801
10	time[Title/Abstract] OR period*[Title/Abstract] OR interval*[Title/Abstract] OR calendar year*[Title/Abstract] N = 3,401,312
11	population[Title/Abstract] N = 936,431
12	risk[Title/Abstract] N = 1,328,908
13	#9 AND #10 AND #11 AND #12 N = 302
17	Limits: adult: 19+ years N = 236
Search strategy using keywords in Embase	
1	Multiple AND primary AND (‘cancer’/exp OR cancer) OR multiple AND primary AND malignanc* OR multiple AND primary AND tumo* OR multiple AND primary AND carcinoma* OR second AND (‘cancer’/exp OR cancer) OR second AND malignanc* OR second AND tumo* OR second carcinoma* N = 236,978

2	Time AND period* OR time AND interval* OR calendar AND year* N = 691,550
2	#1 AND #2 AND population AND risk AND [embase]/lim N = 457

Approach 2

Search strategy using MeSH terms in Medline

No.	Search
1	"Neoplasms, Multiple Primary"[Mesh] OR "Neoplasms, Multiple Primary"[Mesh] OR "Neoplasms, Second Primary"[Mesh] OR "Neoplasms, Second Primary"[Mesh] AND "Risk Assessment"[Mesh] N = 613
2	Limits: adults N = 455

Search strategy using keywords in Medline

1	multiple primary cancer*[Title/Abstract]
2	multiple primary malignanc*[Title/Abstract]
3	multiple primary tumo*[Title/Abstract]
4	multiple primary carcinoma*[Title/Abstract]
5	multiple cancer*[Title/Abstract]
6	multiple malignanc*[Title/Abstract]
7	multiple tumo*[Title/Abstract]
8	multiple carcinoma*[Title/Abstract]
9	second primary cancer*[Title/Abstract]
10	second primary malignanc*[Title/Abstract]
11	second primary tumo*[Title/Abstract]
12	second primary carcinoma*[Title/Abstract]
13	second primary cancer*[Title/Abstract]
14	second primary malignanc*[Title/Abstract]
15	second primary tumo*[Title/Abstract]
16	second primary carcinoma*[Title/Abstract]
17	#1 OR #2 OR #3 OR #4 OR #5 OR #6 OR #7 OR #8 OR #9 OR #10 OR #11 OR #12 OR #13 OR #14 OR #15 OR #16 N = 12,841
18	time OR period* OR year* N = 5,764,460
19	population-based[Title/Abstract]
20	risk[Title/Abstract]
21	#17 AND #18 AND #19 AND #20 N = 232
17	Limits: adult: 19+ years N = 186

3.3.3 Data extraction and analysis

Titles and abstracts of identified articles were assessed against the inclusion criteria by one author (YY). The full text of potentially relevant studies and the reference lists of included studies were read to identify further original articles. Two authors (YY and AV) developed an extraction sheet to record first author's name, publication year, source of data, the number of Strengthening the Reporting of Observational Studies in Epidemiology (STROBE) criteria met, site of first primary cancer, study period and follow-up, study size, study population (definition and inclusion criteria), definition of MPCs, calendar year of first cancer diagnosis, and the standardised incidence ratios (SIRs) or relative risks (RRs) and 95% confidence intervals (95% CIs) for MPCs by time periods. Typically, SIRs were derived from the observed number of MPCs divided by the expected number (O/E), with the expected number calculated from age-, sex- and calendar year- specific incidence rates in the general population [7, 28]. Alternatively, RRs were calculated as the risk of MPCs occurring in one time period compared with a reference period [29].

The STrengthening the Reporting of OBservational studies in Epidemiology (STROBE) criteria were used to assess the strengths, weaknesses, and generalizability of included studies [30]. The STROBE statement was developed to help readers when critically appraising published articles. Two authors (YY and AV) used a modified checklist of items for cohort studies to assess the number of criteria met in each study. We evaluated the coding rules of MPCs (i.e. Surveillance, Epidemiology, and End Results (SEER) [31] or International Association of Cancer Registries (IACR) and the International Agency for Research on Cancer (IARC) (IARC/IACR) [8] coding rules for MPCs) applied in each study as the diagnostic criteria in the STROBE checklist.

3.4 Results

3.4.1 Literature search

The defined search criteria identified 1,832 relevant articles and four were added through manual review of references. Of the 225 articles assessed as eligible for full-text review, 23 articles met the inclusion criteria and were included in the narrative synthesis. After combining five eligible articles in the updated search, 28 studies were included in the final analysis comprising 26 population-based studies and two monographs (Figure 3.1).

3.4.2 Study characteristics

All 28 included studies were population-based, published between 1987 and 2015, presenting data from Europe, North America, Australia and Japan (Table 3.2). 26 were peer-reviewed publications, reporting on more than 2.8 million survivors of adult cancer over the period of 1943 to 2012 [32-57], with 178,091 MPCs identified. Four of them reported the risk of developing MPCs following first cancer with all sites combined [46, 47, 49, 53]. Others focused on the risk of MPCs following first cancer at a specific site. The remaining were two monographs from the USA and Italy. One was a SEER monograph that used data from nine cancer registries in the USA, reported on more than 2 million cancer survivors during the follow-up period from 1973 to 2000, and a total of 185,407 MPCs were observed [7]. The other was a monograph of the Italian Association of Cancer Registries (AIRTUM), using data from 38 general and five specialised cancer registries in Italy, that reported on more than 1.6 million cancer survivors during the period of 1976-2010 with 85,399 MPCs identified [58].

The coding rules to define MPCs varied across studies. Seven studies and the SEER monograph used incidence and follow-up data from SEER program registries, and employed

SEER coding rules [7, 40-45, 54]. Eight studies and the Italian monograph used coding rules proposed by the IARC/IACR [38, 39, 46, 48, 49, 51, 53, 57, 58]. While it may be difficult to directly compare risk estimates derived using different coding rules, comparisons of temporal trends will be valid if the rules used to define MPCs are consistent over time within a single study population [59].

3.4.3 Study quality

The number of STROBE criteria met in all population-based studies ranged from 18 to 28 of 30 items in total, with 21 studies meeting at least 25 criteria. Included studies had various objectives, data sources, study sizes and STROBE criteria met, but they all reported the risk of MPCs over different time periods.

3.4.4 Risk of MPCs following first primary cancer with all sites combined

Six studies reported temporal trends in MPC risk among survivors of adult cancer with all first cancer sites combined. Four of them observed an increasing trend in MPC risk from earlier to more recent periods. The SEER monograph reported a 14% higher risk of developing MPCs than would be expected in the general SEER population during the 25 years of follow-up, with a total of 185,407 observed MPCs compared with 162,602 expected (SIR, 1.14; 95% CI, 1.14 to 1.15). There was an increasing trend of SIRs rising from 1.12 with periods of first cancer diagnosis during 1973-79 to 1.21 during 1995-2000 [7]. Three large population-based studies from Australia, Finland and Japan (Australia and Japan including more than 200,000 cancer survivors, Finland including 470,000 cancer survivors) also showed an increase in the risk of developing MPCs across the whole study period when all first cancer sites are combined. In Australia, the SIRs grew from 1.14 with periods of first

diagnosis in 1982-1986 to 1.46 in 1997-2001 [47]. In Finland, the SIRs increased from 4.96 in the 1950s to 7.64 in the 1980s [53]. In Japan, the relative risk increased from 1.00 in 1966-1971 (reference) to 2.89 in 1984-1986 [46]. However, two studies from Italy and France showed no significant difference in SIRs across different time periods. The Italian monograph reported SIRs of 1.10 in 1978-1987, 1.08 in 1988-1997 and 1.10 in 1998-2010, with a 10% higher risk of developing MPCs than expected across the entire study period 1976-2010 (SIR, 1.10; 95%CI, 1.09 to 1.10) [58]. The French study was a large population-based study using data from 10 French population-based cancer registries, with a first cancer diagnosis between 1989 and 2004 [49].

3.4.5 Risk of MPCs following first primary cancers at specific sites

The risk of MPCs following first cancers at specific sites did not differ significantly across calendar periods of first cancer diagnosis in 14 studies [34, 36, 37, 39-42, 44, 45, 48, 50-52, 56]. Six studies reported an increasing temporal trend in MPC risk [33, 35, 43, 54, 55, 57], whilst two studies reported a decreasing trend in MPC risk after breast cancer during the study period 1943- 2000 [32, 38]. There were a total of three studies on breast cancer as the first cancer.

3.4.5.1 MPCs following leukaemia, lymphoma and myeloma

Eight studies assessed the risk of MPCs following first cancers of the hematopoietic and lymphoid system [33, 35-37, 41, 44, 52, 55]. The risk of MPCs did not reveal any particular trends with respect to variations in SIRs over time in either of two major leukaemia (chronic myeloid leukaemia, chronic lymphocytic leukaemia) [36, 37] or the uncommon hairy cell leukaemia [41, 52]. These studies compared the risk of MPCs before and after a time point around 1990 when novel therapeutics such as interferon, fludarabine and other nucleoside analogues were

introduced. Three studies with first cancers of Hodgkin or non-Hodgkin lymphoma reported an increasing trend in the risk of MPCs over time [33, 35, 55]. The risk of MPCs increased from 1.2 in the 1960s to 1.6 in the 1970s among 3,139 cases of Hodgkin's disease [33]. For MPCs following non-Hodgkin lymphoma (NHL), the risk was higher in the time interval of 2000-2006 (RR=1.00, reference) than in 1980-1984 (RR=0.65; 95%CI: 0.59-0.72) in more than 60,000 registered cases from three Nordic countries [35]. A similar pattern was also confirmed in France. The risk of MPCs was 1.37 (95%CI: 1.08-1.74) times higher for NHL diagnoses in 2000-2004 than in the 1989-1994 reference category [55]. For MPCs following multiple myeloma, there was no significant change in the risk before and after 2000. However, the overall risk of MPCs was also not significant (SIR=0.98; 95% CI: 0.94–1.02) [44].

3.4.5.2 MPCs following breast and ovarian cancer

No statistically significant change or decreasing trends in MPCs risk was observed in three breast cancer studies, two from multicentre studies and one from a single cancer registry [32, 38, 39]. One large multicentre study used data on 525,527 breast cancer survivors from 13 population-based cancer registries from Europe, Australia, Canada and Singapore covering the study period 1943-2000. The risk of MPCs decreased from 1.32 (95%CI 1.30-1.35) before 1975 to 1.18 (95%CI 1.14-1.22) after 1991 [38]. Another multicentre study encompassing four Scandinavian cancer registries reported data on more than 300,000 one-year survivors of breast cancer during a similar period, 1943-2002. The risk of MPCs was lower after 1980 than before (SIR = 1.09 and 1.19, respectively). However, second haematological cancers were excluded from the analysis [32]. No significant change in trend was observed in a study from a single cancer registry in Spain during the period of 1985-2007 (SIR 1.37, 95%CI 1.16-1.58 in 1985-1995 and SIR 1.41, 95%CI 1.18-1.64 in 1996-2007) [39]. The risk of MPCs following ovarian cancer increased from 1.1 in 1961-69 to 1.2 in 1970-80

(no 95%CI provided), using data from a single cancer registry in the UK. However, the observed numbers were mostly too small to obtain reliable estimates [33].

3.4.5.3 MPCs following thyroid cancer

In the USA, the risk of MPCs was higher in patients diagnosed with a first thyroid cancer during 2004-2008 (SIR 1.45, 95%CI 1.28-1.62) than in 1973-1983 (SIR 1.02, 95%CI 0.97-1.07) [43]. In Korea, however, the risk only reached statistical significance for a first thyroid cancer diagnosis between 2003 and 2007 (SIR 1.09, 95%CI 1.03-1.15), with smaller increases in other periods (SIR= 0.92 in 1993-1997, 1.05 in 1998-2002 and 1.06 in 2008-2010).

3.4.5.4 MPCs following prostate cancer

Interestingly, the risk of MPCs following a first prostate cancer was significantly lower than expected in two relevant studies from the USA and Korea [34, 56]. The value of SIRs was consistently 0.7 from 1974 to 1994 using data from SEER (USA) cancer registries [34] and ranged from 0.6 to 0.7 during 1993-2011 using data from a nationwide hospital-based cancer registry in Korea [56].

3.4.5.5 MPCs following first cancers at other sites

From the early 1970s to the mid-2000s, the temporal trends in the risk of MPCs did not change significantly with a first cancer diagnosis of malignant meningioma, oesophageal cancer and ocular melanoma [40, 45, 48], but varied for first cancer at head and neck [51]. The risk of MPCs following testicular cancer remained consistent and lower than expected from 1961 to 1980. Although the SIRs for first cancer of Merkel Cell carcinoma increased from 1.09

(95%CI 0.83-1.70) in 1986-1994 to 1.37 (95%CI 1.05-1.76) in 1995-2002, the increase was not statistically significant [42]. For MPCs following colorectal cancer and bladder cancer, both risks increased with the year of first cancer diagnosis. The SIRs increased significantly from 1.53 (95%CI 1.37-1.71) in 1989-1992 to 2.02 (95%CI 1.79-2.27) in 2001-2004 for first bladder cancer [57]. For first cancer at colon and rectum, the SIRs were higher in 2002-2012 (1.25 for colon, 1.16 for rectum) than in 1992-2001 (1.08 for colon, 1.00 for rectum) [54].

Figure 3.1: Flow diagram of study selection

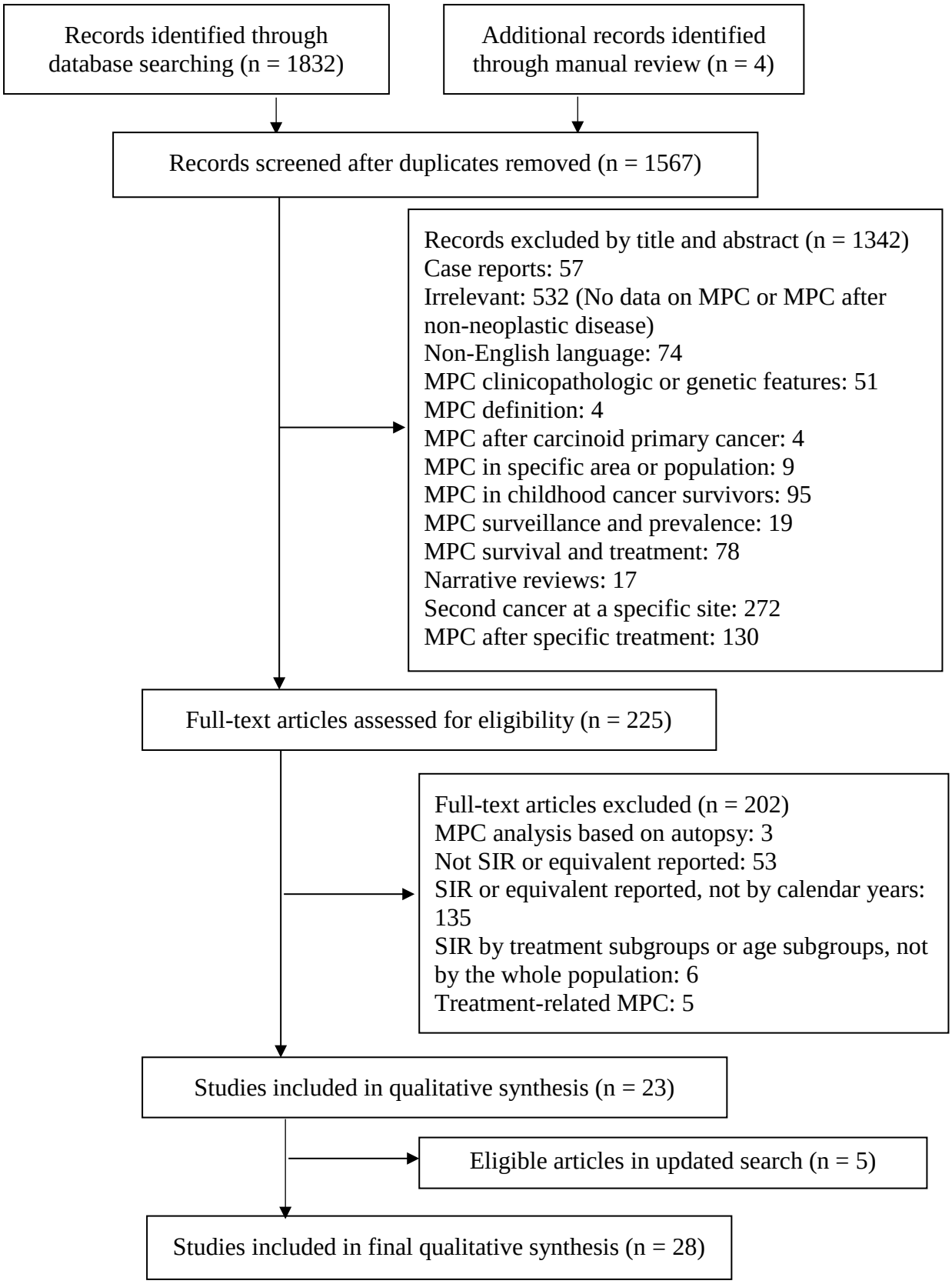

Table 3.2: MPCs following a first primary cancer at any site or a specific site

First author, Publication year, Institute,	STROBE criteria (met/ total criteria)	First cancer diagnosis	Design Study period Follow-up	Patients, N	Patients with MPCs, N	Study population: definition and inclusion criteria	Definition of MPCs: inclusion criteria	Calendar year of first cancer diagnosis	Standardised incidence ratio (95%CI)	Relative risk (95%CI)
Any site										
Curtis RE et al (2006) SEER, U.S.	27/30	Any site	1973-2000	More than 2 million	185,407	The study population includes nearly 2 million cancer patients reported to the 9 SEER registries from 1973 to 2000, with follow-up for subsequent cancer occurrence extending up to 27 years.	MPC coding rules: SEER	1973-1979 1980-1984 1985-1989 1990-1994 1995-2000	1.12 1.14 1.14 1.14 1.21	
AIRTUM Working Group (2013) Italian Association of Cancer Registries, Italy	27/30	Any site	1976-2010	1,635,060	85,399	This monograph uses data from the AIRTUM Database (at December 2012) regarding all cancer cases, except non-melanoma skin cancer, diagnosed between 1976 and 2010 in the general cancer registries.	MPC coding rules: IARC/IACR rules	1978-1987 1988-1997 1998-2010	1.10(1.09-1.11) 1.08(1.07-1.10) 1.10(1.09-1.12)	
Jégu J et al (2014) 10 French population-based cancer registries, France	28/30	Any site	1989-2004 Followed up to 2007	289,967	21,226	All patients presenting with a first cancer diagnosed between 1989 and 2004, excluding non-melanoma skin cancers.	MPC coding rules: IARC/IACR rules	1989-1994 1995-1999 2000-2004	1.39(1.36-1.42) 1.36(1.33-1.39) 1.34(1.30-1.37)	

Youlden DR et al (2011) Queensland Cancer Registry, Australia	26/30	Any site	1982-2001 Followed up to 2006	204,962	23,580	All patients diagnosed with a first primary invasive cancer between 1982 and 2001 who survived for a minimum of 2 months, restricting to 15 years or older at the time of first diagnosis.	MPC coding rules: Included histologically similar cases of cancer at the same body site. Excluded synchronous primary cancers (those diagnosed within 2 months of the first primary cancer)	1982-1986 1987-1991 1992-1996 1997-2001	1.14(1.08-1.20) 1.22(1.17-1.28) 1.36(1.31-1.41) 1.46(1.41-1.50)	
Sankila R et al (1995) Finnish Cancer Registry, Finland	22/30	Any site	1953-1991	470,000	19,800	All 470,000 patients registered in Finland from 1953 to 1991 with malignant neoplasms [primary site codes 140-208 in the International Classification of Diseases (ICD-7), WHO, 19571 excluding basal-cell carcinomas of the skin, carcinoma in situ of the uterine cervix, and papilloma of the urinary organs.	MPC coding rules: IARC/IACR rules	1953-1959 1960-1969 1970-1979 1980-1991	4.96 6.10 8.63 7.64	
Tsukuma H et al (1994) Osaka Cancer Registry, Japan	18/30	Any site	1966-1986 Followed up to 1989	217,307	4,436	All reported cases aged 0-79 who were initially diagnosed with a first primary cancer (invasive cancer and benign intracranial tumour)	MPC coding rules: IARC/IACR rules	1966-1971 1972-1977 1978-1983 1984-1986	Ratio of SIRs 1.00(reference) 1.59(1.33-1.90) 2.89(2.47-3.38) 2.89(2.45-3.40)	
Specific site										
leukaemia, lymphoma and myeloma										

Rebora P et al (2010) Swedish Cancer Registry, Sweden	23/30	Chronic myeloid leukaemia	1970-1995 Followed up to 2007	2,753	145	All adult cases of CML as a primary diagnosis (ICD-7 code 205.1, age at diagnosis ≥ 18 years) arising between January 1, 1970, and December 31, 1995.	MPC coding rules: not specified.	1970-1984 1985-1995	1.68(1.32-2.12) 1.97(1.55-2.48)	
Schöllkopf C et al (2007) Danish Cancer Register, Denmark	24/30	Chronic lymphocytic leukaemia	1943-2003	12,373	1,105	All patients with chronic lymphocytic leukaemia (ICD-7-code 204.0)	MPC coding rules: not specified. Excluding second cancers diagnosed less than one year after CLL	1943- 1994 1994- 2003	1.62(1.50-1.76) 1.55(1.41-1.69)	
Hisada M et al (2007) SEER, U.S.	26/30	Hairy cell leukaemia	1973-2002	3104	358	All hairy cell leukaemia patients who survived for at least 2 months after diagnosis.	MPC coding rules: SEER	1973-1989 1990-2002	1.17(1.01-1.36) 1.30(1.12-1.51)	
Federico M et al (2002) The nationwide registry of the Italian Cooperative Group, Italy	22/30	Hairy cell leukaemia	1981-1996	952	49	Patients were recorded in the Italian Registry of HCL between January 1981 and December 1996.	MPC coding rules: not specified.	1978-1982 1983-1987 1988-1992 1993-1999	1.00(0.27-2.57) 0.89(0.36-1.84) 1.04(0.62-1.65) 1.02(0.62-1.58)	

M.P. Coleman et al (1987) South Thames (now Thames) Cancer Registry, UK	28/30	Hodgkin's disease	1961-1980 Followed up to 1981	2,970	58	All patients registered with Hodgkin's disease in the South Thames Cancer Registry during the period 1961-80. Excluded patients if they had had another tumour registered either before or at the same time as the index tumour, or if their index tumour had been registered at death (no follow-up) or at age 85 years or more.	Second cancer defined as the site and the histology are distinct from the first. Second cancers at the same site as the first or at a different site but with the same histology as the first will be registered only if the hospital record or pathology report explicitly states that it is a new primary, distinct from the previous cancer. Excluded second tumours occurring at age 85 or over.	1961-1969 1970-1980	1.2 1.6	
Lorenzo Bermejo J et al (2014) Cancer registries of Finland, Norway and Sweden	22/30	non-Hodgkin lymphoma	1980-2006	21,036 Finnish, 14,027 Norwegian 25,838 Swedish	6815	Almost all histologically confirmed cases of non-Hodgkin lymphoma.	MPC coding rules: not specified	1980-84 1985-89 1990-94 1995-99 2000-06		0.65(0.59-0.72) 0.71(0.66-0.77) 0.77(0.72-0.83) 0.77(0.73-0.82) Reference

Rossi C et al (2015) 10 French population-based cancer registries, France	25/30	non-Hodgkin lymphoma	1989-2004 Followed up to 2007	7,546	580	NHL patients was extracted from the K2 France cohort, which includes cancer cases diagnosed between 1989 and 2004 recorded by 10 French population based cancer registries. Patients who developed a synchronous second cancer (<61 days of follow-up) were excluded.	MPC coding rules: A Second Primry Cancer was defined as the first subsequent primary cancer occurring at least two months (≥61 days) after the first diagnosis of NHL.	1989-1994 1995-1999 2000-2004	Ratio of SIRs 1.00(reference) 1.07(0.86-1.34) 1.37(1.08-1.74)	
Razavi P et al (2013) SEER, U.S.	28/30	Multiple myeloma	1973-2008	36,491	2021	All cases were identified by site code ICD-0-3: C9732 and C9734. Excluded cases whose reporting sources were coded as autopsy or death-certificate-only (n=775), cases where MM was not the first primary (n=3545) and cases with second cancer diagnosed within the first 2 months of MM diagnosis (n=365)	MPC coding rules: SEER All second cancers except cancers within the first two months after diagnosis of MM	1973-1984 1985-1999 2000-2008	1.04(0.95-1.13) 0.95(0.90-1.02) 0.96(0.88-1.06)	
Breast and ovarian cancer										

Mellemkjaer L et al (2006) 13 population-based cancer registries Europe, Australia, Canada and Singapore	26/30	Breast cancer	1943-2000	525,527	31,399	All women with a first primary breast cancer (ICD-9 5 174) except patients for whom the first primary cancer diagnosis and death were recorded at the same time or who had 2 first primary cancers recorded simultaneously (same dates of diagnosis).	MPC coding rules: IARC/IACR Second cancers except contralateral breast cancer, brain and nervous system only included malignant tumours, bladder cancer included papilloma, included all non-melanoma skin cancer	<1975 1975-1983 1984-1990 1991+	1.32(1.30-1.35) 1.22(1.20-1.25) 1.23(1.20-1.26) 1.18(1.14-1.22)	
Brown LM et al (2007) Population-based cancer registries in Denmark, Finland, Norway and Sweden	27/30	Breast cancer	1943-2002	376,825	23,158	All women diagnosed with a first primary cancer of the breast between January 1, 1943 and December 31, 2002 who survived at least 1 year.	MPC coding rules: Subsequent primary non-haematological malignancies (except breast cancer) that developed at least 1 year after breast cancer diagnosis	<1980 ≥1980	1.19[a] 1.09[a] [a] Confidence interval does not include 1.0	
Molina-Montes E et al (2013) Granada Cancer Registry, Spain	26/30	Breast cancer	1985-2007	5897	314	All cases were identified by site code ICD-O-3 (C50). Exclude patients whose first primary cancer diagnosis and death were recorded simultaneously and synchronous first primary cancers.	MPC coding rules: IACR/IARC All second primary cancers except contralateral breast cancer which considered as a single tumour.	1985-1995 1996-2007	1.37(1.16-1.58) 1.41(1.18-1.64)	

M.P. Coleman et al (1987) South Thames (now Thames) Cancer Registry, UK	28/30	Ovarian cancer	1961-1980 Followed up to 1981	11,802	170	All patients registered with cancer of the ovary in the South Thames Cancer Registry during the period 1961-80. Excluded patients if they had had another tumour registered either before or at the same time as the index tumour, or if their index tumour had been registered at death (no follow-up) or at age 85 years or more.	Second cancer defined as the site and the histology are distinct from the first. Second cancers at the same site as the first or at a different site but with the same histology as the first will be registered only if the hospital record or pathology report explicitly states that it is a new primary, distinct from the previous cancer. Excluded second tumours occurring at age 85 or over.	1961-1969 1970-1980	1.1 1.2	
Thyroid cancer										
Cho YY et al (2015) Korean Central Cancer Registry, Korea	25/30	Thyroid cancer	1993-2010	178,844	2,895	Records code C73.9 starting in January 1993 through December 2010. Patients who developed a second malignancy within the first 2 months of follow-up (n=628) were excluded.	MPC coding rules: not specified.	1993-1997 1998-2002 2003-2007 2008-2010	0.98(0.90-1.07) 1.05(0.98-1.13) 1.09(1.03-1.15) 1.06(0.96-1.17)	
Kim C et al (2013) SEER, U.S.	24/30	Thyroid cancer	1973-2008	52,103	4457	All cases were identified by site code ICD-0-3: C739, reported to a SEER 9 database between 1973-2008	MPC coding rules: SEER All second cancers except cancers within the first two months after initial thyroid cancer	1973-1983 1984-1993 1994-2003 2004-2008	1.02(0.97-1.07) 1.03(0.97-1.08) 1.21(1.14-1.28) 1.45(1.28-1.62)	
Prostate cancer										

Joung JY et al (2015) Korean Central Cancer Registry, Korea	22/30	Prostate cancer	1993-2011	55,378	2,578	Patients diagnosed with a first prostate cancer between 1993 and 2011. Excluded patients who presented with a SPC within two months of their first prostate cancer diagnosis, patients with subsequent prostate cancer after the diagnosis of another primary cancer, and patients for whom only death certificate information was available.	MPC coding rules: not specified	1993-2000 2001-2011	0.6 0.7	
Levi F et al (1999) Vaud and Neuchâtel Cancer Registry, Switzerland	26/30	Prostate carcinoma	1974-1994	4,503	380	Cases of first diagnosed prostate carcinoma registered between 1974 and 1994 with histologic confirmation available for 89.7%.	MPC coding rules: not specified	1974-1984 1985-1994	0.7(0.6-0.8) 0.7(0.6-0.8)	
Other sites (malignant meningioma, head and neck, oesophageal, ocular melanoma, merkel cell, colorectal cancer, bladder, testis)										
Bao X et al (2014) SEER, U.S.	26/30	Malignant meningioma	1973-2007	1,603	56	All patients in the SEER database with the diagnosis of malignant meningioma were identified via SEER program 6.6.2 (1973–2007).	MPC coding rules: SEER	1973-1988 1989-1999 2000-2007	0.78 1.01 0.56	

Jégu J et al (2013) Bas-Rhin population based cancer registry, France	28/30	Head and neck squamous cell carcinomas	1975-2006	7,329	1,326	All patients were followed-up for 10 years or until December 31, 2006. HNSCC included here were squamous cell carcinomas (ICD-O-3 histology codes 8070–8076, 8078) localized at the oral cavity, oropharynx, hypopharynx and larynx (ICD-O-3 site codes C01–C06, C09–C10, C12–C13, C32).	MPC coding rules: IARC/IACR rules	1975-1979 1980-1984 1985-1989 1990-1994 1995-1999 2000-2006	Ratio of SIRs 1.00(reference) 1.15(0.95-1.40) 1.29(1.06-1.55) 1.25(1.03-1.51) 1.10(0.90-1.35) 0.85(0.67-1.08)	
Zhu G et al (2012) SEER, U.S.	25/30	Oesophageal cancer	1973-2007	24,557	985	All oesophageal cancer patients who survived for at least 2 months after diagnosis.	MPC coding rules: SEER All second primary cancers except non-melanoma skin cancers	1973-1989 1990-2007	1.43(1.29-1.58) 1.28(1.18-1.38)	
Scélo G et al (2007) 13 population-based cancer registries Europe, Australia, Canada and Singapore	25/30	Ocular melanoma	1943-2000	10,396	1,029	All cases of ocular melanoma without stratifying by subsite.	MPC coding rules: IARC/IACR rules	<1975 1975-1983 1984-1990 1991+	1.17(1.06-1.29) 1.21(1.08-1.35) 1.39(1.20-1.59) 1.33(1.08-1.62)	
Howard RA et al (2006) SEER, U.S.	26/30	Merkel cell carcinoma	1986-2002	1,306	122	All patients with a first primary cutaneous MCC in 1 of 11 population-based cancer registries of SEER program (1986-2002).	MPC coding rules: SEER Subsequent primary cancers were invasive primary neoplasms that developed at least 1 month after a diagnosis of MCC. Excluded secondary MCC following primary MCC.	1986-1994 1995-2002	1.09(0.83-1.40) 1.37(1.05-1.76)	

Guan X et al (2015) SEER, U.S.	23/30	Colorectal cancer	1992-2012	240,584	27,731	Invasive CRC patients who were diagnosed at the age of more than 20 years. Excluded patients: 1) diagnosed with unknown age, 2) reported only on death or autopsy certificate only, 3) being stage of in situ. SPMs diagnosed during six months period after the primary diagnosis were also excluded.	MPC coding rules: SEER	Colon 1992-2001 2002-2012 Rectum 1992-2001 2002-2012	 1.08 1.25 1.00 1.16	
Muller J et al (2015) 10 French population-based cancer registries, France	28/30	Bladder cancer	1989-2004 Followed up to 2007	10,047	1,291	All patients with a first bladder cancer (BCa) diagnosed between 1989 and 2004 and followed up to 31 December 2007. Excluded patients with a known history of previous cancer before BCa diagnosis	MPC coding rules: IARC/IACR rules	1989-1992 1993-1996 1997-2000 2001-2004	1.53(1.37-1.71) 1.42(1.27-1.58) 1.57(1.41-1.74) 2.02(1.79-2.27)	

M.P. Coleman et al (1987) South Thames (now Thames) Cancer Registry, UK	28/30	Testicular cancer	1961-1980 Followed up to 1981	2,013	27	All patients registered with cancer of the testis in the South Thames Cancer Registry during the period 1961-80. Excluded patients if they had had another tumour registered either before or at the same time as the index tumour, or if their index tumour had been registered at death (no follow-up) or at age 85 years or more.	Second cancer defined as the site and the histology are distinct from the first. Second cancers at the same site as the first or at a different site but with the same histology as the first will be registered only if the hospital record or pathology report explicitly states that it is a new primary, distinct from the previous cancer. Excluded second tumours occurring at age 85 or over.	1961-1969 1970-1980	0.8 0.7	
STROBE= STrengthening the Reporting of OBservational studies in Epidemiology. MPCs=Multiple Primary Cancers. N=number of patients. SEER=Surveillance, Epidemiology, and End Results. IARC/IACR= International Association of Cancer Registries (IACR)/the International Agency for Research on Cancer (IARC). CI=confidence interval. ICD=International Classification of Diseases. CML= Chronic Myeloid Leukaemia. CLL=Chronic Lymphocytic Leukaemia. MM=Multiple Myeloma. MCC=Merkel Cell Carcinoma.										

3.5 Discussion

To our knowledge, this is the first systematic review focusing on the temporal trends in the risk of MPCs. There was an increasing time trend in the risk of developing MPCs in the USA and Australia when all first cancer sites were combined. Risk increased from 1.12-1.14 following a first cancer diagnosis in the early 1980s, to 1.21-1.46 in the late 1990s. In European countries, the risk remained similar during 1978-2010 for Italian cancer survivors and showed no significant change between 1989 and 2004 for French cancer survivors. Three potential explanations are postulated for the increasing trends in the USA and Australia: 1) increased detection of MPCs, both intended and incidental; 2) increased radiation exposure and 3) changed cancer treatments. The trends in the risk of developing MPCs varied by site of first cancer from 1943 to 2012, but mostly there was little change.

3.5.1 Increased detection

Increasing risk of MPCs might be a result of increased detection arising from the introduction of cancer screening programs for the early detection of cancers in the community; and incidental findings arising from the increased use of sensitive imaging tests in the routine clinical follow-up of cancer survivors. Early detection and incidental findings are not necessarily of benefit, as they can lead to "overdiagnosis". Overdiagnosis is the detection of a "cancer" that would not cause symptoms or death in a patient's lifetime [60].

Higher MPCs risk was observed in studies from the USA and Australia in the late 1990s [7, 47]. These findings coincide with the introduction of national cancer screening programs for cervical cancer and breast cancer in Australia in the early 1990s [61]. In the USA, the use of cancer screening for cervical cancer, breast cancer, colorectal cancer and prostate cancer has

increased since 1987, particularly for breast cancer [62-64]. As well as providing benefits, screening has led to the overdiagnosis of non-progressive or low progressing cancers [65-68].

Cancer survivors are considered at increased risk for future cancers, and screening has been specifically recommended for survivors of some cancer types [69]. A meta-analysis of 20 studies demonstrated that cancer survivors tended to receive more frequent screening for new primary cancers, especially for breast, cervical, colorectal and prostate cancer than non-cancer controls [70]. This may thus differentially lead to increased detection among cancer survivors compared with the general population.

Another activity leading to a higher rate of MPCs may be the increased use and improvements in diagnostic imaging in recent time periods. The use of diagnostic imaging, especially computed tomography (CT) scans, has increased dramatically worldwide since 1980, particularly in the USA, Australia and Japan [9, 11, 71]. Cancer survivors routinely undergo CT scanning and other imaging procedures during follow-up, the detection of a new primary cancer, therefore, becomes more likely than in the general population with no prior cancer diagnosis [72]. Some of these incidental findings might be clinically unimportant, leading to overdiagnosis [10, 60, 73].

3.5.2 Increased radiation exposure during the follow-up after a first cancer diagnosis

Radiation exposure due to monitoring may of itself lead to harmful effects [74]. This possibility is consistent with our finding that the highest risk of MPCs, from the late 1990s, has occurred since radiation exposure has increased enormously [9]. Since the 1980s, the average annual per-capita effective dose from medical radiological procedures doubled worldwide [9, 11]. In the USA, the average annual per capita dose for medical procedures increased almost six-fold

from 0.5mSv in 1980 to 3.0mSv in 2006 [9], with X-rays and CT scan the two most common imaging procedures leading to radiation exposure [11].

The lifetime risk of cancer attributable to diagnostic X-rays is estimated to vary between 0.6% and 1.8% across 15 countries, including the USA and Australia, between 1991 and 1996 [75]. In Japan, the attributable risk has been estimated at 3.2%, but the Japanese results are confounded by the impact of background radiation following the atomic bombings in World War II [75].

CT scanning has been widely used since the 1990s and delivers a much higher radiation dose than diagnostic X-rays [76]. In Australia, the cancer risk in children and adolescents who underwent CT scanning between 1985-2005 was found to be 24% higher than in their peers who did not undergo CT scanning [16]. The impact on lifetime risk could not be ascertained given that cancer excess was still occurring at the end of the study. Increased risk of cancer due to CT scanning is not, however, limited to children. Adults are also at increased risk of cancer from the radiation exposure [77]. Imaging-based evaluation, especially CT scans, is the preferred modality to assess response to treatment, and for routine surveillance of most cancer survivors [78]. Therefore, increased risk of MPCs could be partly attributable to cumulative radiation exposure due to recurrent CT scans [79].

3.5.3 Changed cancer treatments

Studies of MPCs consequent to a primary cancer at a specific site can help us understand the impact of treatment changes on trends of MPC risk. No statistically significant change in risk of MPC was observed in most specific site studies, including after the 1990s when many newer (and improved) treatments or management strategies were introduced [34, 36, 37, 39-42, 44, 45, 52, 56]. A decrease in risk was observed in two of three breast cancer studies, which may reflect

the improvement in radiation techniques [32, 38]. On the other hand, an increase in MPC risk was observed for a first non-Hodgkin lymphoma diagnosis in the mid-2000s than in the early 1990s, which may suggest an adverse treatment effect with increased use of nucleoside analogues (e.g. Fludarabine) at the end of the 1990s [35, 55]. The increase in the risk of MPCs following thyroid cancer might occur as a consequence of aggressive radiation treatment [43]. This is particularly concerning in regard to the more recent increased detection and treatment of microcarcinoma [80], largely considered to encompass overdiagnosis and overtreatment [73].

Together these findings suggest that most treatments have not impacted the baseline risk of MPCs in persons recently diagnosed with a primary cancer (post-1990), with the exceptions of breast cancer (reduction), non-Hodgkin lymphoma and thyroid cancer (increase).

3.5.4 Other factors to be considered

Changing patterns in lifestyle or environmental risk factors may also affect the value of SIRs over time. Temporal trends in population exposure to carcinogenic factors such as alcohol and tobacco consumption, differed across countries [49]. Any differences over time in exposure in the reference population compared with the population of cancer survivors could contribute to changing SIRs.

3.5.5 Limitations

Several factors limit the interpretation of our findings. First, studies of all first cancer sites combined from the USA and Australia did not cover the last 15 years. This period is of particular relevance given the introduction of nuclear medicine imaging, for example, PET/CT scanning. Second, cancer survivor profile (age at first cancer diagnosis, site of first cancer) may have varied according to year of first cancer diagnosis and these factors may

contribute to changing SIRs [49]. For example, cancer survivor profiles have changed with the implementation of cancer screening programs. Third, variation in screening guidelines, follow-up care, management and treatment for cancer across countries potentially affect the generalizability of the results. Fourth, some included studies did not clearly specify the coding rules or definition of MPCs, which may result in misclassification and less reliable estimation of the observed number of MPCs. Fifth, different timeframes of the study cohorts may limit the ability to evaluate long-term effects of changing patterns in medical surveillance and treatment of the primary cancer. Some studies published before 2000 lack sufficient data to compare SIRs pre-1990s and post-1990s when treatment improved [33, 34, 46, 53]. Sixth, articles in languages other than English were excluded, which could lead to language bias. Last, although we defined the age of the study population as adults, some studies, mostly those using SEER cancer registries, reported across all ages [7, 33, 35, 37, 40-46, 48, 50, 53, 55, 58]. However, childhood cancer survivors accounted for a limited proportion of all cancer survivors (no more than 2% in SEER cancer registries), and the types of cancer developed in children were limited [7], which should minimise any impact on the overall results.

3.5.6 Conclusion

The overall risk of developing MPCs appears to have increased in the USA and Australia from the 1980s to 2000 when all first cancer sites are combined. Increased detection due to the more frequent use of diagnostic imaging and increased medical radiation exposure may be potential explanations. Studies from Italy and France, however, showed no significant change in MPC risk in patients diagnosed with a first cancer after 2000. Given the implementation of new cancer screening programs and the growth of nuclear medical imaging (e.g. PET/CT scanning) since 2000, continued long-term surveillance is needed from

non-European as well as European countries. Future studies are needed to assess the extent of overdiagnosis and overtreatment among cancer survivors relative to the general population, and thus to assess whether there is potential for optimising follow-up strategies.

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Chapter 4: Temporal trends in the risk of second primary cancers among survivors of adult-onset cancers, 1980-2013: An Australian population-based study

4.1 Abstract

Background: Our systematic review indicated an increasing trend in the risk of second primary cancers (SPCs) from the 1980s to 2000 when considering studies from the USA and Australia. It is uncertain whether this trend has continued to increase since 2000.

Methods: Population-based study of 51,802 individuals with adult-onset cancers identified in the Tasmanian Cancer Registry. Patients with a first cancer diagnosis between 1980-2009 were followed up to December 2013. SPC risks were quantified using standardized incidence ratios (SIRs) and absolute excess risks (AERs). Trends in SPC risk were assessed in multivariable Poisson models.

Results: With a median follow-up of 4.8 years (mean=6.9 years), 5,339 SPCs were observed. The SIRs for any SPC increased from 0.98 (95%CI, 0.90-1.07) after a first cancer diagnosis in 1980-1984 to 1.12 (95%CI, 1.05-1.20) in 2005-2009. In multivariable Poisson models accounting for patient sex, age at first cancer diagnosis, follow-up intervals and first cancer types, the trend in SIRs increased significantly from 1980-2009 for all SPCs ($P_{trend} < 0.001$) and for specific SPCs of head and neck, lung, digestive tract and prostate (all $P_{trend} < 0.05$). From 2000 onwards, the AER for specific SPCs after specific first cancers was highest for prostate cancer after first cancers of the urinary tract (AER, 54.3/10,000 person-years).

Conclusion: In Tasmania, the risk of SPCs among survivors of adult-onset cancers has increased with periods of first cancer diagnosis from 1980-2009. Increased cancer screening and improved medical imaging may have contributed to the greater risk in recent years.

Key words: Second primary cancers, risk, trends, adult-onset cancer survivors, population-based.

4.2 Introduction

Survivors of adult-onset cancer are at risk of developing second primary cancers (SPCs) [1, 2] and have been reported to have a 7%-36% higher cancer risk than expected in the general population [3-7]. Our recent systematic review of temporal change in subsequent cancer risk indicated an increasing trend in the risk among adult cancer survivors from the 1980s to 2000 when considering studies from the USA and Australia but not from elsewhere [8]. However, few studies have more than 20 years' surveillance to assess time patterns on overall SPC risks into the most recent era [5].

Factors associated with changing trends in SPC risk might include increased detection of SPCs and changing patterns of cancer treatment or other shared carcinogenic factors (e.g. tobacco and/or alcohol consumption). Both radiotherapy and chemotherapy can induce treatment-related cancers but evidence suggests this explains a relatively small proportion of SPCs in adults [9, 10].

Cancer survivors tend to undergo repeated medical imaging for treatment response evaluation and post-treatment surveillance. In addition, they may receive more frequent screening for new cancers than people without a history of cancer [11]. While patients are expected to benefit from follow-up care, they may also be more likely to have indolent cancers or "incidentalomas" detected leading to cancer overdiagnosis [12]. The use of diagnostic imaging and cancer screening tests has increased sharply in Australia and other developed countries (e.g. the USA) since the 1980s [13-15]. Studies from Australia and the USA have observed a gradual increase in SPC risk over the period 1982-2001 and 1973-2000 as a potential consequence [3, 4]. It is unclear if the risk of SPCs has continued to increase since then.

To better understand trends in SPC risk, this study aimed to (i) investigate changes in SPC risk over time in survivors of adult-onset cancer in Tasmania, an island state of Australia with limited out-migration [16]; and (ii) assess any changes in SPC burden in survivors of specific types of first cancer during the recent three decades.

4.3 Methods

4.3.1 Study population

This study included 51,802 cancer patients identified in the Tasmanian Cancer Registry (TCR). They were diagnosed with a first cancer at age 15 years or older from 1980 to 2009, and survived at least two months. Follow-up of the cohort ended on December 31, 2013. The TCR is a population-based registry covering the entire state. Most registered cases include data from both pathology laboratories and hospital services (inpatient or radiation oncology clinic) [17]. Access to de-identified records was approved by Tasmanian Health and Medical Human Research Ethics Committee.

4.3.2 Ascertainment of SPCs

Ascertainment of SPCs followed the International Rules for Multiple Primary Cancers (ICD-O Third Edition) proposed by the International Association of Cancer Registries (IACR) and the International Agency for Research on Cancer (IARC) [18]. SPCs occurring within 2 months of the date of first cancer diagnosis were excluded to reduce detection bias. Site and morphology for first primary cancers and SPCs were coded using the International Classification of Disease for Oncology, Third Edition (ICD-O3). Cancers of different sites were grouped as shown in Table 4.1. We only included cases of invasive cancer; cases of

benign tumours, cancers in situ or of uncertain behaviour were all excluded. Non-melanoma skin cancers (NMSC) were also excluded as they are not routinely registered in the TCR.

4.3.3 Statistical analysis

Using a standard person-years approach [19, 20]. person-years at risk (PYR) was assessed from 2 months after the first cancer diagnosis to the date of second cancer diagnosis, the date of death, or the end of follow-up (31 December 2013), whichever came first. PYR for each patient in the study cohort were accumulated within specific sex, 5-year age group and 1-year calendar period strata. The expected number of SPCs (E) was calculated using PYR within strata multipled by corresponding site-specific cancer incidence rates in the Tasmanian population.

4.3.3.1 Comparisons with the general population

Standardized incidence ratios (SIR) were calculated as the ratios of observed to expected numbers of SPCs (O/E). Poisson regression models were used to derive 95% confidence intervals (95%CIs) of SIRs, assuming that the observed number followed a Poisson distribution [3, 19, 20]. It has been suggested that including SPCs occurring in the same site as the first cancer leads to underestimation of SIRs for all sites of SPC combined [21]. For example, SPCs of the same anatomical site as a first cancer are very rare in prostate cancer patients, leading to a lower number of observed SPCs (the SIR numerator). To maintain consistency with IARC coding rules that neoplasms diagnosed simultaneously in the same site of different morphology should be regarded as multiple cancers, here we aimed to describe the risk of all SPCs rather than second discordant primary cancers. SIRs were stratified by first cancer types, second cancer types and calendar year of first cancer diagnosis on 5-year

intervals (1980-1984, 1985-1989, 1990-1994, 1995-1999, 2000-2004, 2005-2009). Absolute excess risks (AER) were calculated by subtracting the expected number of second cancers from the observed number, then dividing by 10,000 person years ([O− E]/[PYR × 10,000]) [3, 22]. The AER is interpreted as the absolute measure of SPC burden in a specific population of cancer survivors [3, 23]. For survivors of specific first cancer types, we computed the SIRs and AERs by three calendar periods of first cancer diagnosis (1980-1989, 1990-1999 and 2000-2009) to identify the types of SPC that contributed changes in SPC burden during the recent three decades.

4.3.3.2 Internal comparisons within the study cohort

We used multivariable Poisson regression models to estimate trends and heterogeneity in SIRs within the study cohort by categories of sex, age at first cancer diagnosis (15-49, 50-64, 65-84, 85+ years), period of first diagnosis (1980-1984, 1985-1989, 1990-1994, 1995-1999, 2000-2004 and 2005-2009), follow-up intervals (<1 year, 1-4 years, 5-9 years, 10+ years) and first cancer sites [10, 22]. The P-value for trend was estimated using the likelihood ratio test. We also analysed the data using negative binomial regression to test the robustness of the Poisson regression model. The results were almost identical so we only present results derived from the Poisson regression model. A two-sided P value less than 0.05 was considered as statistically significant. All analyses were performed using Stata software (version 12; StataCorp LLC, College Station, Texas).

4.4 Results

4.4.1 Characteristics of the study population

A total of 5,339 SPCs were identified among the 51,803 eligible cancer patients who accumulated 347,830 person-years at risk during 1980-2013 (Table 4.1). The mean age of patients at the first cancer diagnosis was 64.3 years (median 66.2 years). The occurrence of SPCs was most common among those diagnosed with their first cancer between the ages of 65-84 years. The mean follow-up was 6.9 years (median 4.8 years; 25th-75th percentiles, 1.2-10.2 years). In terms of absolute numbers, SPCs occurred most frequently in patients with a first diagnosis of prostate cancer (n=986), colorectal cancer (n=827), skin cancer (excluding NMSC) (n=658) and breast cancer (n=635). The most commonly observed SPCs were colorectal cancer (n=848), lung cancer (n=761), prostate cancer (n=694) and cancers of digestive tract excluding colorectal cancer (n=563) (Table 4.2).

Table 4.1: Characteristics of the study population

Characteristics	Patients		Person-years at risk	Second Primary Cancers (all sites combined)	
	No.	%		No.	%
Total	51,802	100.0	347,830	5,339	100.0
Sex					
Male	28,242	54.5	166,051	3,334	62.4
Female	23,560	45.5	181,779	2,005	37.6
Age at first cancer diagnosis, years					
15-49	8,508	16.4	99,178	577	10.8
50-64	15,687	30.3	117,907	1,760	33.0
65-84	24,916	48.1	124,345	2,866	53.7
85+	2,691	5.2	6,400	136	2.5
Period of first cancer diagnosis					
1980-1984	5,252	10.1	41,245	513	9.6
1985-1989	6,241	12.1	50,517	707	13.2
1990-1994	8,370	16.2	67,350	1,009	18.9
1995-1999	9,429	18.2	71,361	1,119	21.0
2000-2004	10,176	19.6	63,504	1,078	20.2
2005-2009	12,334	23.8	53,853	913	17.1
Maximum follow-up					
2 months – less than 1 year	11,270	21.7	37,701	584	11.0
1 – 4 years	15,263	29.5	127,597	1,901	35.6
5 – 9 years	11,954	23.1	92,894	1,427	26.7
≥10 years	13,315	25.7	89,638	1,427	26.7
Type of first cancer (ICD-O codes)					
Head and neck (C00 - C14, C30-C32)	2,525	4.9	19,366	473	8.9
Digestive organs, except colorectal (C15-C17, C22-C26)	3,460	6.7	7,366	141	2.6
Colorectal (C18-C21)	7,567	14.6	47,229	827	15.5
Lung and Thymus (C33-C34, C37-C38)	5,010	9.7	9,075	151	2.8
Haematological systems* (C42)	2,165	4.2	10,930	282	5.3
Skin§ (C44)	5,046	9.7	53,929	658	12.3
Breast (C50)	6,833	13.2	65,749	635	11.9
Female organs (C51-C58)	2,590	5.0	23,593	252	4.7
Prostate (C61)	7,924	15.3	52,384	986	18.5
Urinary tract (C64-C68)	3,077	5.9	21,063	465	8.7
All lymphoma(C77)	1,913	3.7	14,343	229	4.3
Others	3,692	7.1	22,803	240	4.5

* Malignancies in haematological systems means all malignancies in the hematopoietic and reticuloendothelial systems using the "C42" ICD-O-3 code. § The reported data includes melanoma of the skin and the invasive non-melanoma skin cancers such as Merkel Cell Carcinomas. The more common non-melanoma skin cancers, Basal Cell Carcinomas and Squamous Cell Carcinomas (SCCs) are not registered by the Tasmanian Cancer Registry, and therefore not included in these analyses.

Table 4.2: Number of second primary cancers, by type of first and second cancer

	Second primary cancer type											
First primary cancer	**All sites**	**Head and neck**	**Digestive, except colorectal**	**Colorectal cancer**	**Lung cancer**	**Haematological + Lymphoma**	**skin cancer**	**Breast cancer**	**Female organs**	**Prostate cancer**	**Urinary cancer**	**Others**
Head and neck	473	62	50	46	116	32	27	15	1	76	25	23
Digestive, except colorectal	141	5	24	14	21	6	12	7	4	28	16	4
Colorectal	827	28	90	73	121	57	80	66	21	182	68	41
Lung and Thymus	151	17	27	20	8	16	8	6	3	28	10	8
Haematological systems	282	10	23	28	35	48	42	12	4	46	12	22
Skin	658	34	57	105	57	60	23	74	24	141	32	51
Breast	635	20	66	137	75	57	74	10	101	3	41	51
Female organs	252	6	18	59	37	21	10	52	7	0	21	21
Prostate	986	45	128	242	158	123	108	2	0	2	116	62
Urinary tract	465	17	41	54	81	39	27	19	9	131	25	22
All lymphoma	229	8	13	36	24	38	26	22	5	26	11	20
Others	240	9	26	34	28	21	25	25	7	31	17	17
All sites	5339	261	563	848	761	518	462	310	186	694	394	342

4.4.2 SPCs at any site

For the whole study period, the SIR of any SPC was 1.06 (95%CI 1.03-1.09) and AER was 8.7/10,000 person-years. The SIRs increased from 0.98 (95%CI, 0.90-1.07) with a first cancer diagnosis in 1980-1984 to 1.12 (95%CI, 1.05-1.20) in 2005-2009 (Table 4.3).

We did a sensitivity analysis to examine the effect of including SPCs occurring within two months of a first cancer diagnosis and of excluding SPCs within four months of a first cancer diagnosis on SIRs by 5-year calendar periods. Both the overall SIRs and the time patterns were similar to the main results when SPCs in the first 2 months were excluded. The overall SIR was 1.08 (95%CI 1.05-1.10) for all SPCs and 1.05 (95%CI 1.02-1.08) when we excluded SPCs occurring within 4 months. The SIRs increased from 0.98 (95%CI 0.90-1.07) in 1980-1984 to 1.20 (95%CI 1.13-1.28) in 2005-2009 with all SPCs included. The SIRs increased from 0.98 (95%CI 0.90-1.07) in 1980-1984 to 1.11 (95%CI 1.04-1.19) in 2005-2009 when excluding SPCs within 4 months.

There was a significantly increasing temporal trend in the SIRs for any SPC, with adjustments for patient sex, age at first diagnosis, follow-up interval and first cancer type (adjusted $P_{trend} < 0.001$) (Figure 4.1). We checked the trends across single calendar years and found a significant increasing trend in SPC risk in the multivariable Poisson model ($P_{trend} < 0.001$). We also assessed potential non-linear associations in the model. The goodness of fit did not significantly improve after adding a quadratic term for single-year to the model (likelihood-ratio test, P = 0.6826), therefore suggesting a linear trend across single-year periods. The multivariable Poisson models revealed that age at first cancer diagnosis, period of first diagnosis, and first cancer type were independently associated with the risk of any SPC (all *P* values < 0.05) (Table 4.4). To reduce the risk of residual confounding due to

different follow-up intervals, we assessed the pattern of risk over time after restricting the follow up interval for all cases to a maximum of 9 years. The same patterns were apparent for SIRs by period of first cancer diagnosis and in the multivariable Poisson model adjusting for sex, age at first cancer diagnosis and first cancer types.

Analysis by specific first cancer types revealed various changes in SPC risk over time (Table 4.5). The SIRs for all SPCs were highest for individuals with a first cancer diagnosis of head and neck cancer in 2005-2009 and the trend in SIRs increased over time ($P_{trend} = 0.040$). The trends in SIRs for any SPC also increased over time for individuals with a first diagnosis of skin cancer, prostate cancer and cancers of the urinary tract (all $P_{trend} < 0.05$).

4.4.3 SPCs at specific sites

For individuals with a first diagnosis of any cancer type, the SIRs for a second cancer of the digestive tract including colorectal cancer, were significantly elevated in more recent periods compared to earlier periods (all $P_{trend} < 0.05$) (Table 4.6). The SIRs for prostate cancer after any first cancer tended to decline over time. However, after adjustment for age at first diagnosis, follow-up interval and first cancer type, the risk of prostate cancer as a SPC increased significantly over time (adjusted $P_{trend} = 0.013$) (Figure 4.1). Individuals with any first cancer diagnosis in recent periods were also more likely to have a SPC diagnosis of head and neck cancer, digestive cancer (including colorectal cancer) and lung cancer compared to earlier periods after adjusting for sex, age at first diagnosis, follow-up interval and first cancer type (all adjusted $P_{trend} < 0.05$) (Figure 4.1).

Table 4.7 shows SIR and AER estimates for SPCs following a first cancer diagnosis in 1980-1989, 1990-1999 and 2000-2009 for specific first cancer and SPC types where the observed

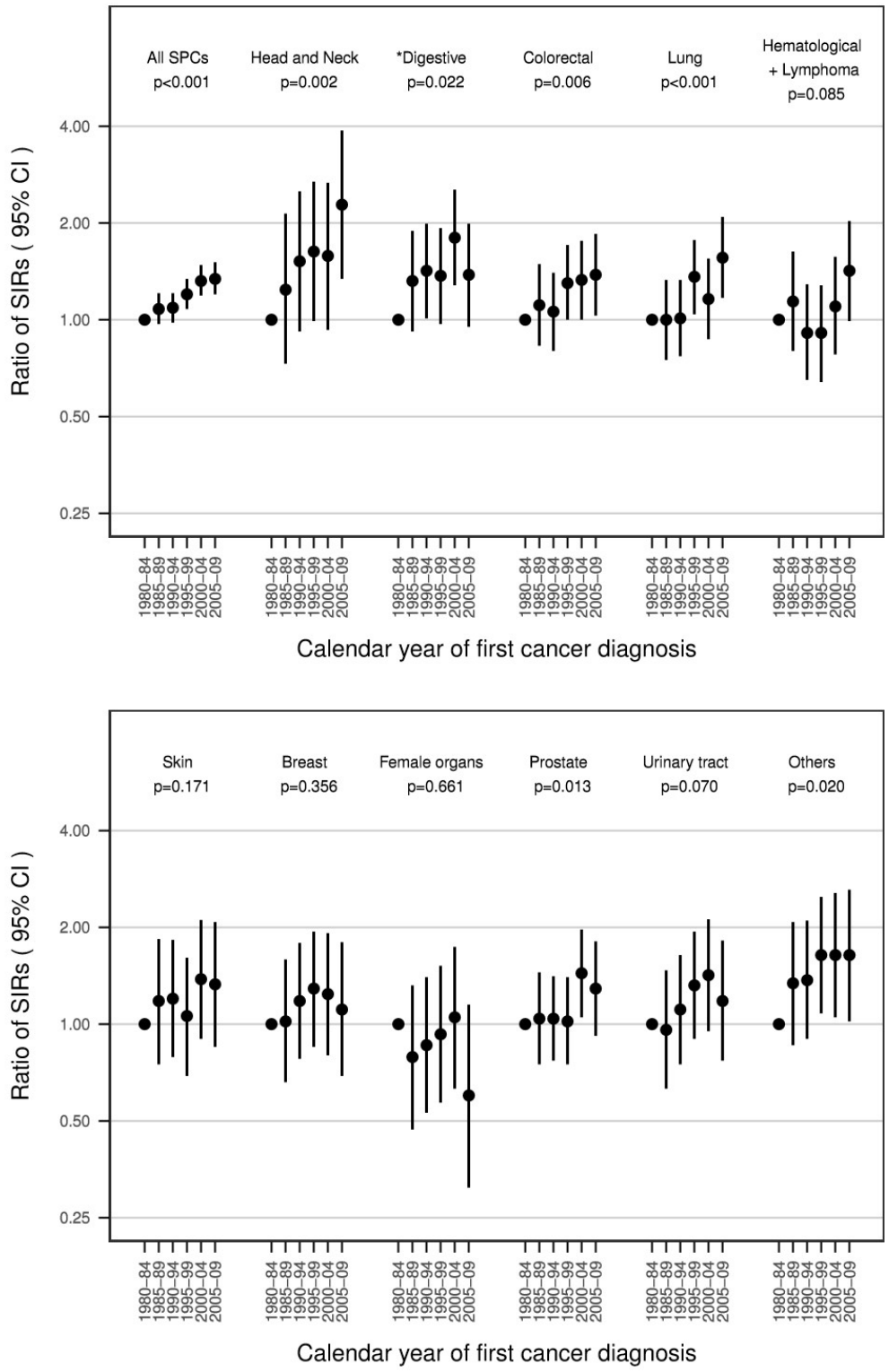
number of relevant SPCs was at least 50 and AER value for at least one of the three periods was more than 5 cases per 10,000 PYR. For individuals with a first diagnosis of head and neck cancer, lung cancer accounted for the largest AER in both the earlier and more recent periods but AERs for prostate cancer showed the greatest increase in AERs from 1980-1989 to 2000-2009 (AERs increased from -7.1/10,000 PYR to 15.0/10,000 PYR). Both the SIRs and AERs for SPCs of the head and neck continued to increase from 1980 to 2009 among survivors of first head and neck cancer. For survivors of first cancers of the urinary tract, prostate cancer contributed most to SPC burden in 2000-2009 with a striking increase in relevant AERs (from 0.5/10,000 PYR in 1980-1989 to 54.8/10,000 PYR in 2000-2009). Prostate cancer was also responsible for the greatest SPC burden among survivors of skin cancer in 2000-2009 (AER, 15.0/10,000 PYR). Colorectal cancer contributed most to the SPC burden in 2000-2009 among survivors of first cancers of female reproductive organs. However, there was a decrease in the relevant AERs from 1980-1989 (8.5/10,000 PYR) to 1990-1999 (3.8/10,000 PYR) before an increase to 2000-2009 (AER, 18.3/10,000 PYR). For colorectal cancer survivors, the SPC that demonstrated the greatest increase in AERs was skin cancer, the AERs increased from 1.2/10,000 PYR in 1980-1989 to 12.5/10,000 PYR in 2000-2009.

Table 4.3: Temporal trends of standardized incidence ratios (SIRs) for all second primary cancers in Tasmania, 1980-2009.

Calendar periods of first cancer diagnosis	No. of First Primary Cancers	Person-years at Risk	Observed Second Primary Cancers	Expected Second Primary Cancers	SIR (95%CI)
1980-2009	51,802	347,830	5,339	5,036	**1.06** (1.03 to 1.09)
1980-1984	5,252	41,245	513	521	0.98 (0.90 to 1.07)
1985-1989	6,241	50,517	707	677	1.04 (0.97 to 1.12)
1990-1994	8,370	67,350	1,009	1025	0.98 (0.93 to 1.05)
1995-1999	9,429	71,361	1,119	1057	**1.06** (1.00 to 1.12)
2000-2004	10,176	63,504	1,078	941	**1.15** (1.08 to 1.22)
2005-2009	12,334	53,853	913	815	**1.12** (1.05 to 1.20)
******P* trend					**<0.001**

******P*-value was derived from multivariable Poisson regression models with adjustment for sex (not for female organs and prostate), age at first cancer diagnosis, follow-up intervals and first cancer types. Bold numbers indicated statistically significance.

Figure 4.1: Ratio of SIRs for all SPCs and specific SPC types after any first cancer by calendar periods of first cancer diagnosis.



P-values were derived from multivariable Poisson regression models with adjustment on sex (not for female organs and prostate), age at first cancer diagnosis, follow-up intervals and first cancer types. *For digestive cancers, colorectal cancers were excluded.

Table 4.4: Multivariable Poisson regression for Ratio of SIRs for all SPCs and specific SPC types

	All	Head and neck	Digestive, except colorectal	Colorectal	Lung	Haematological and lymphoma
	Adjusted SIRs (95%CI)	Adjusted SIRs (95%CI)	Adjusted SIRs (95%CI)	Adjusted SIRs (95%CI)	Adjusted SIRs (95%CI)	Adjusted SIRs (95%CI)
Sex						
Male	1.00 (ref)	1.00 (ref)	1.00 (ref)	1.00 (ref)	1.00 (ref)	1.00 (ref)
Female	0.99 (0.92-1.06)	1.24 (0.87-1.76)	1.06 (0.85-1.33)	1.06 (0.87-1.29)	1.14 (0.93-1.39)	1.11 (0.81-1.34)
P heterogeneity	0.762	0.245	0.590	0.576	0.224	0.362
Age at first cancer diagnosis, y						
15-49	1.00 (ref)	1.00 (ref)	1.00 (ref)	1.00 (ref)	1.00 (ref)	1.00 (ref)
50-64	0.96 (0.87-1.05)	0.95 (0.63-1.41)	0.70 (0.50-0.98)	0.75 (0.58-0.96)	0.79 (0.60-1.05)	1.00 (0.72-1.40)
65-84	0.93 (0.84-1.02)	0.89 (0.59-1.35)	0.59 (0.42-0.83)	0.73 (0.57-0.95)	0.67 (0.50-0.90)	0.96 (0.69-1.34)
85+	0.71 (0.58-0.86)	1.00 (0.43-2.33)	0.51 (0.30-0.88)	0.78 (0.51-1.22)	0.31 (0.15-0.64)	0.86 (0.48-1.54)
P trend	0.012	0.633	0.002	0.054	<0.001	0.649
Period of first cancer diagnosis						
1980-1984	1.00 (ref)	1.00 (ref)	1.00 (ref)	1.00 (ref)	1.00 (ref)	1.00 (ref)
1985-1989	1.08 (0.97-1.21)	1.24 (0.73-2.14)	1.32 (0.92-1.89)	1.11 (0.83-1.49)	1.00 (0.75-1.33)	1.14 (0.80-1.63)
1990-1994	1.09 (0.98-1.21)	1.52 (0.92-2.51)	1.42 (1.01-1.99)	1.06 (0.80-1.40)	1.01 (0.77-1.33)	0.91 (0.65-1.29)
1995-1999	1.20 (1.08-1.34)	1.63 (0.99-2.69)	1.37 (0.97-1.93)	1.30 (1.00-1.71)	1.36 (1.04-1.77)	0.91 (0.64-1.28)
2000-2004	1.32 (1.19-1.48)	1.58 (0.93-2.67)	1.80 (1.28-2.54)	1.33 (1.00-1.76)	1.16 (0.87-1.55)	1.10 (0.78-1.57)
2005-2009	1.34 (1.20-1.51)	2.28 (1.34-3.88)	1.38 (0.95-1.99)	1.38 (1.03-1.85)	1.56 (1.17-2.09)	1.42 (0.99-2.03)
P trend	<0.001	0.002	0.022	0.006	<0.001	0.085
Maximum follow-up						
2 – 11 months	1.00 (ref)	1.00 (ref)	1.00 (ref)	1.00 (ref)	1.00 (ref)	1.00 (ref)
1 – 4 y	0.97 (0.88-1.06)	1.59 (0.98-2.59)	1.05 (0.79-1.39)	1.01 (0.79-1.29)	1.04 (0.80-1.34)	1.17 (0.85-1.61)
5 – 9 y	0.99 (0.89-1.09)	1.98 (1.19-3.27)	1.03 (0.76-1.39)	1.01 (0.78-1.31)	1.16 (0.89-1.51)	1.24 (0.89-1.74)
≥10 y	1.05 (0.94-1.16)	1.90 (1.10-3.26)	0.82 (0.59-1.14)	1.10 (0.84-1.44)	1.04 (0.78-1.39)	1.28 (0.89-1.83)
P trend	0.090	0.072	0.083	0.426	0.720	0.292

Continued

Type of first cancer						
Head and neck	1.00 (ref)	1.00 (ref)	1.00 (ref)	1.00 (ref)	1.00 (ref)	1.00 (ref)
Digestive, except colorectal	0.74 (0.61-0.89)	0.23 (0.09-0.58)	1.15 (0.71-1.89)	0.72 (0.39-1.31)	0.47 (0.29-0.75)	0.46 (0.19-1.10)
Colorectal	0.65 (0.58-0.73)	0.20 (0.12-0.31)	0.64 (0.45-0.91)	0.54 (0.37-0.78)	0.40 (0.31-0.52)	0.62 (0.40-0.96)
Lung and Thymus	0.63 (0.53-0.76)	0.64 (0.37-1.10)	1.09 (0.68-1.74)	0.86 (0.51-1.47)	0.13 (0.07-0.28)	1.04 (0.57-1.90)
Haematological systems	1.02 (0.88-1.19)	0.31 (0.16-0.61)	0.76 (0.46-1.25)	0.99 (0.62-1.59)	0.55 (0.38-0.81)	2.48 (1.58-3.90)
Skin	0.69 (0.61-0.78)	0.29 (0.19-0.44)	0.58 (0.40-0.86)	1.08 (0.76-1.54)	0.27 (0.19-0.37)	0.91 (0.59-1.40)
Breast	0.58 (0.51-0.66)	0.20 (0.11-0.36)	0.58 (0.38-0.86)	1.05 (0.73-1.52)	0.31 (0.22-0.43)	0.68 (0.43-1.09)
Female organs	0.72 (0.61-0.85)	0.19 (0.08-0.47)	0.50 (0.29-0.89)	1.41 (0.93-2.13)	0.48 (0.32-0.72)	0.75 (0.42-1.34)
Prostate	0.47 (0.42-0.53)	0.18 (0.12-0.27)	0.60 (0.43-0.84)	1.28 (0.93-1.77)	0.31 (0.24-0.40)	0.95 (0.64-1.41)
Urinary tract	0.79 (0.69-0.90)	0.24 (0.14-0.41)	0.65 (0.43-0.99)	0.93 (0.63-1.38)	0.57 (0.43-0.75)	0.97 (0.61-1.55)
All lymphoma	0.89 (0.76-1.05)	0.25 (0.12-0.52)	0.48 (0.26-0.89)	1.37 (0.89-2.13)	0.40 (0.26-0.62)	2.11 (1.32-3.39)
Others	0.76 (0.65-0.89)	0.21 (0.10-0.43)	0.82 (0.51-1.32)	1.09 (0.70-1.71)	0.40 (0.26-0.61)	0.97 (0.56-1.69)
P heterogeneity	<0.001	<0.001	0.006	<0.001	<0.001	<0.001

Note: P-values were derived from multivariable Poisson regression models with adjustment on sex (not for female organs and prostate), age at first cancer diagnosis, follow-up intervals and first cancer types.

Table 4.5: Standardized incidence ratios (SIRs) for specific first cancer types by calendar year of first cancer diagnosis, 1980-2013

	Calendar year of first cancer diagnosis, y																		
	1980-1984			1985-1989			1990-1994			1995-1999			2000-2004			2005-2009			
First cancer sites	No. Obs	SIR (95% CI)	AER	No. Obs	SIR (95% CI)	AER	No. Obs	SIR (95% CI)	AER	No. Obs	SIR (95% CI)	AER	No. Obs	SIR (95% CI)	AER	No. Obs	SIR (95% CI)	AER	P-trend in SIR
Head and neck	68	1.46 (1.15 to 1.85)	74.2	77	1.50 (1.20 to 1.87)	77.6	85	1.40 (1.13 to 1.74)	66.3	94	1.59 (1.30 to 1.95)	89.3	90	1.83 (1.49 to 2.25)	122.1	59	1.91 (1.48 to 2.46)	124.9	0.040
Digestive, except colorectal	14	1.18 (0.70 to 1.99)	26.3	13	0.79 (0.46 to 1.35)	-33.0	25	1.05 (0.71 to 1.55)	8.7	33	1.53 (1.09 to 2.16)	88.4	32	1.39 (0.98 to 1.96)	62.7	24	1.04 (0.70 to 1.56)	7.3	0.443
Colorectal	86	0.84 (0.68 to 1.04)	-25.9	127	1.02 (0.86 to 1.22)	3.9	154	0.96 (0.82 to 1.13)	-6.9	181	1.13 (0.98 to 1.31)	23.5	155	1.12 (0.96 to 1.31)	21.1	124	1.04 (0.88 to 1.24)	7.2	0.057
Lung	13	0.87 (0.50 to 1.49)	-18.5	20	0.88 (0.57 to 1.36)	-18.4	34	1.01 (0.72 to 1.42)	2.4	26	0.99 (0.68 to 1.46)	-1.4	28	0.98 (0.68 to 1.42)	-3.6	30	1.27 (0.89 to 1.82)	45.8	0.219
Haematological	19	1.43 (0.91 to 2.25)	57.9	45	1.81 (1.35 to 2.42)	128.2	48	1.50 (1.13 to 1.99)	87.8	45	1.62 (1.21 to 2.17)	93.1	53	1.34 (1.02 to 1.75)	55.2	72	2.08 (1.65 to 2.62)	166.2	0.383
Lymphoma	29	1.46 (1.01 to 2.09)	45.0	43	1.73 (1.28 to 2.33)	74.5	38	1.23 (0.89 to 1.69)	25.0	48	1.51 (1.14 to 2.01)	9.1	44	1.54 (1.14 to 2.06)	10.1	27	1.19 (0.81 to 1.73)	23.9	0.465
skin	49	0.90 (0.68 to 1.19)	-9.5	82	0.95 (0.76 to 1.18)	-5.1	114	0.96 (0.80 to 1.16)	-4.0	139	1.11 (0.94 to 1.31)	12.4	156	1.37 (1.17 to 1.61)	42.8	118	1.37 (1.15 to 1.64)	44.8	<0.001
Breast	62	0.85 (0.66 to 1.09)	-15.3	91	0.88 (0.72 to 1.08)	-13.0	136	0.97 (0.82 to 1.14)	-3.5	136	0.96 (0.81 to 1.14)	-3.8	131	0.97 (0.82 to 1.15)	-3.4	79	0.95 (0.76 to 1.18)	-5.3	0.393
Female organs	54	1.09 (0.83 to 1.42)	8.5	46	1.04 (0.78 to 1.39)	3.8	56	1.31 (1.01 to 1.71)	30.2	33	0.87 (0.61 to 1.22)	-12.1	33	1.18 (0.84 to 1.67)	17.8	30	1.48 (1.03 to 2.11)	47.6	0.390
Prostate	36	0.69 (0.50 to 0.96)	-75.7	54	0.64 (0.49 to 0.83)	-103.2	181	0.70 (0.60 to 0.80)	-84.7	252	0.80 (0.71 to 0.91)	-49.5	220	0.80 (0.70 to 0.92)	-48.0	243	0.81 (0.72 to 0.92)	-38.8	0.039
Urinary tract	46	0.89 (0.67 to 1.19)	-18.1	73	1.14 (0.91 to 1.43)	25.3	96	1.13 (0.92 to 1.38)	24.7	15	1.30 (1.06 to 1.59)	52.7	78	1.54 (1.23 to 1.92)	88.8	79	1.56 (1.25 to 1.95)	94.2	<0.001
Other	37	1.19 (0.86 to 1.64)	15.9	36	1.22 (0.88 to 1.70)	19.7	42	1.15 (0.85 to 1.55)	12.2	39	0.93 (0.68 to 1.27)	-6.2	58	1.81 (1.40 to 2.34)	68.4	28	1.24 (0.85 to 1.79)	20.8	0.276
Total	513	0.98 (0.90 to 1.07)	-2.0	707	1.04 (0.97 to 1.12)	6.0	1009	0.98 (0.93 to 1.05)	-2.3	1119	1.06 (1.00 to 1.12)	8.7	1078	1.15 (1.08 to 1.22)	21.6	27	1.12 (1.05 to 1.20)	18.2	0.001

P values for trends in SIRs were derived from univariable Poisson regression models. Bold numbers indicated statistically significance.

Table 4.6: Standardized incidence ratios (SIRs) for specific second cancer types by calendar year of first cancer diagnosis, 1980-2013.

	Calendar year of first cancer diagnosis, y																		
	1980-1984			1985-1989			1990-1994			1995-1999			2000-2004			2005-2009			
Second cancer sites	No. Obs	SIR (95% CI)	AER	No. Obs	SIR (95% CI)	AER	No. Obs	SIR (95% CI)	AER	No. Obs	SIR (95% CI)	AER	No. Obs	SIR (95% CI)	AER	No. Obs	SIR (95% CI)	AER	P-trend in SIR
Head and neck	22	1.05 (0.69 to 1.59)	0.2	33	1.27 (0.90 to 1.79)	1.4	54	1.37 (1.05 to 1.79)	2.2	56	1.42 (1.09 to 1.84)	2.3	45	1.35 (1.01 to 1.81)	1.8	51	1.63 (1.24 to 2.15)	3.7	0.104
Digestive, except colorectal	48	0.96 (0.72 to 1.27)	-0.5	75	1.24 (0.99 to 1.56)	2.9	112	1.29 (1.07 to 1.55)	3.8	109	1.24 (1.03 to 1.49)	2.9	130	1.70 (1.43 to 2.02)	8.4	89	1.30 (1.05 to 1.59)	3.8	0.016
Colorectal	79	0.94 (0.75 to 1.17)	-1.3	107	1.02 (0.84 to 1.23)	0.4	148	0.97 (0.83 to 1.14)	-0.7	191	1.19 (1.03 to 1.37)	4.3	168	1.19 (1.02 to 1.38)	4.2	155	1.22 (1.04 to 1.43)	5.2	0.008
Lung	86	1.28 (1.03 to 1.58)	4.5	99	1.20 (0.99 to 1.47)	3.3	135	1.10 (0.93 to 1.30)	1.9	181	1.43 (1.23 to 1.65)	7.6	127	1.19 (1.00 to 1.42)	3.2	133	1.50 (1.26 to 1.77)	8.2	0.138
Haematological and lymphoma	52	1.27 (0.97 to 1.67)	2.7	78	1.47 (1.18 to 1.84)	5.0	89	1.15 (0.94 to 1.42)	1.8	93	1.13 (0.93 to 1.39)	1.5	101	1.39 (1.14 to 1.68)	4.4	105	1.74 (1.44 to 2.11)	8.3	0.090
skin	30	0.97 (0.68 to 1.39)	-0.2	53	1.17 (0.89 to 1.53)	1.5	88	1.19 (0.97 to 1.47)	2.1	89	1.04 (0.84 to 1.28)	0.5	109	1.36 (1.13 to 1.64)	4.5	93	1.30 (1.06 to 1.59)	3.9	0.121
Breast	36	0.65 (0.47 to 0.90)	-4.8	45	0.63 (0.47 to 0.84)	-5.2	61	0.67 (0.52 to 0.87)	-4.4	70	0.75 (0.59 to 0.95)	-3.3	58	0.69 (0.53 to 0.89)	-4.1	40	0.67 (0.49 to 0.91)	-3.7	0.648
Female organs	29	1.23 (0.85 to 1.77)	1.3	29	1.03 (0.72 to 1.49)	0.2	37	1.16 (0.84 to 1.60)	0.8	38	1.23 (0.90 to 1.70)	1.0	38	1.37 (1.00 to 1.89)	1.6	15	0.75 (0.45 to 1.24)	-0.9	0.671
Prostate	60	0.82 (0.63 to 1.05)	-3.3	89	0.80 (0.65 to 0.98)	-4.4	138	0.64 (0.54 to 0.75)	-11.6	124	0.57 (0.48 to 0.68)	-13.1	161	0.78 (0.67 to 0.91)	-7.1	122	0.63 (0.53 to 0.75)	-13.2	0.256
Urinary tract	39	1.19 (0.87 to 1.63)	1.5	47	1.10 (0.83 to 1.47)	0.9	78	1.23 (0.98 to 1.53)	2.2	90	1.40 (1.14 to 1.72)	3.6	80	1.41 (1.13 to 1.75)	3.6	60	1.23 (0.96 to 1.59)	2.1	0.341
Other	32	0.78 (0.55 to 1.10)	-2.2	52	1.02 (0.77 to 1.33)	0.2	69	0.97 (0.77 to 1.23)	-0.3	78	1.14 (0.91 to 1.42)	1.3	61	1.10 (0.86 to 1.41)	0.9	50	1.10 (0.84 to 1.45)	0.9	0.106
Total	513	0.98 (0.90 to 1.07)	-2.0	707	1.04 (0.97 to 1.12)	6.0	1009	0.98 (0.93 to 1.05)	-2.3	1119	1.06 (1.00 to 1.12)	8.7	1078	1.15 (1.08 to 1.22)	21.6	27	1.12 (1.05 to 1.20)	18.2	0.001

P values for trends in SIRs were derived from univariable Poisson regression models. Bold numbers indicated statistically significance.

Table 4.7: Standardized incidence ratios (SIRs) and absolute excess risks (AERs) for selected second cancer types, by first cancer types and periods of first cancer diagnosis, 1980-1989, 1990-1999 and 2000-2009.

		Calendar periods of first cancer diagnosis													
		1980-1989					1990-1999					2000-2009				
First cancer sites	**Second cancer sites**	**No. Obs**	**Person-Years**	**SIR**	**(95%CI)**	**AER**	**No. Obs**	**Person-Years**	**SIR**	**(95%CI)**	**AER**	**No. Obs**	**Person-Years**	**SIR**	**(95%CI)**	**AER**
Head and neck	Head and neck	16	6174	**3.31**	(2.03 to 5.40)	18.1	25	7612	**4.70**	(3.17 to 6.95)	25.9	21	5,581	**6.12**	(3.99 to 9.39)	31.5
	Digestive, except colorectal	19		**2.11**	(1.35 to 3.31)	16.2	14		1.40	(0.83 to 2.36)	5.2	17		**2.53**	(1.57 to 4.07)	18.4
	Lung	38		**2.67**	(1.95 to 3.68)	38.5	45		**3.04**	(2.27 to 4.07)	39.7	33		**3.81**	(2.71 to 5.36)	43.6
	Prostate	19		0.81	(0.52 to 1.27)	-7.1	27		0.88	(0.60 to 1.28)	-4.8	30		1.39	(0.97 to 1.98)	15.0
Colorectal	Digestive, except colorectal	22	13733	0.99	(0.65 to 1.50)	-0.2	40	18214	**1.40**	(1.03 to 1.91)	6.2	28	15,282	1.25	(0.86 to 1.81)	3.6
	Lung	34		1.16	(0.83 to 1.63)	3.5	54		**1.40**	(1.07 to 1.82)	8.4	33		1.13	(0.80 to 1.58)	2.4
	skin	15		1.12	(0.68 to 1.86)	1.2	24		1.02	(0.68 to 1.52)	0.2	41		**1.88**	(1.38 to 2.55)	12.5
	Prostate	39		1.02	(0.75 to 1.40)	0.5	81		**1.26**	(1.01 to 1.56)	9.1	62		1.15	(0.90 to 1.48)	5.4
Skin	Digestive, except colorectal	8	14673	0.68	(0.34 to 1.36)	-2.5	22	22208	1.13	(0.74 to 1.71)	1.1	27	17,048	**1.66**	(1.14 to 2.43)	6.3
	Colorectal	25		1.16	(0.78 to 1.72)	2.3	40		1.12	(0.82 to 1.53)	2.0	40		1.34	(0.98 to 1.82)	5.9
	Haematological	15		1.37	(0.83 to 2.27)	2.8	17		0.92	(0.57 to 1.48)	-0.7	28		**1.83**	(1.27 to 2.65)	7.5
	Breast	16		0.81	(0.50 to 1.32)	-2.5	27		1.02	(0.70 to 1.49)	0.3	31		**1.60**	(1.12 to 2.27)	6.8
	Prostate	24		1.28	(0.86 to 1.91)	3.6	50		1.09	(0.83 to 1.44)	1.9	67		**1.62**	(1.27 to 2.05)	15.0
Breast	Colorectal	35	16937	1.09	(0.78 to 1.51)	1.7	63	27020	**1.31**	(1.03 to 1.68)	5.6	39	21,792	1.08	(0.79 to 1.48)	1.4
	Female organs	30		**1.81**	(1.26 to 2.58)	7.9	44		**1.82**	(1.35 to 2.44)	7.3	27		1.43	(0.98 to 2.08)	3.7
Female organ	Colorectal	25	10025	**1.52**	(1.03 to 2.25)	8.5	17	8661	1.24	(0.77 to 2.00)	3.8	17	4,906	**2.12**	(1.32 to 3.41)	18.3
	Breast	13		**0.58**	(0.33 to 0.99)	-9.5	26		1.26	(0.86 to 1.85)	6.2	13		1.02	(0.59 to 1.75)	0.5
Prostate	Digestive, except colorectal	9	5108	0.69	(0.36 to 1.33)	-7.9	56	21701	1.15	(0.89 to 1.50)	3.4	63	25,574	**1.30**	(1.01 to 1.66)	5.7
	Colorectal	24		1.34	(0.90 to 1.99)	11.8	98		**1.25**	(1.02 to 1.52)	8.9	120		**1.43**	(1.19 to 1.71)	14.1
	Haematological	15		1.51	(0.91 to 2.51)	10.0	46		1.09	(0.82 to 1.46)	1.8	62		**1.49**	(1.16 to 1.91)	7.9
	Urinary	11		0.97	(0.54 to 1.75)	-0.7	60		**1.44**	(1.12 to 1.86)	8.5	45		1.15	(0.86 to 1.54)	2.2
Urinary tract	Colorectal	10	6562	0.57	(0.31 to 1.06)	-11.4	23	8400	1.00	(0.66 to 1.50)	0.0	17	6,102	1.35	(0.88 to 2.07)	8.9
	Lung	26		**1.62**	(1.10 to 2.38)	15.2	38		**1.92**	(1.40 to 2.64)	21.7	17		1.49	(0.93 to 2.40)	9.2
	Prostate	26		1.01	(0.69 to 1.49)	0.5	46		1.13	(0.84 to 1.51)	6.2	59		**2.31**	(1.79 to 2.98)	54.8
All sites combined	All sites combined	1,220	91,761	1.02	(0.96 to 1.08)	2.4	2,128	138,711	1.02	(0.98 to 1.07)	3.3	1,991	117,358	**1.13**	(1.09 to 1.18)	20.0

Bold numbers indicated statistically significance.

4.5 Discussion

In this population-based study with more than 30 years surveillance, the risk of SPC continued to increase beyond 2000 among adult-onset cancer survivors after accounting for background cancer occurrence in the general population and patient characteristics (sex, age at first cancer diagnosis, follow-up intervals and first cancer types) within the study cohort. In particular, the SPC burden due to prostate cancer increased greatly in male survivors of head and neck cancer, skin cancer and cancers of the urinary tract. Site-specific time trends in SPC risk may reveal changing patterns of medical surveillance after a first cancer diagnosis.

Several factors need to be considered in interpreting the results. First, some SPCs may be misclassified as metastases and vice versa. This issue is inevitable in clinical practice and may be more intractable when new cancers arise at the same site and with the same morphology as the first cancer. Applying IARC rules helps to partially avoid this issue as SPCs that originate in the same site and with the same morphology as the first were excluded. As such, using IARC rules resulted in coding fewer SPCs compared to using other coding rules (e.g. Surveillance, Epidemiology, and End Results (SEER) rules) for paired organs (e.g. breast cancer) and therefore, produced lower SIR values [24]. Second, the first cancers diagnosed in 1980-1984 might be second or higher-order cancer in a few cases. The TCR was established in 1978 but records were not as complete in the first two years. Third, the TCR did not record cancer risk factors, treatment data and follow-up procedures making it difficult to investigate the factors that might have contributed to the increase in SPC risk over time. Fourth, the exclusion of SPCs occurring within two months of a first cancer diagnosis may have introduced error but our sensitivity analysis including all SPCs, and excluding SPCs occurring within four months, showed similar results. Additionally, there is the possibility

that multiple testing of stratified data may increase the likelihood of significant differences by chance alone.

Previous studies have reported substantially elevated risk of SPCs among head and neck cancer survivors, with head and neck cancer and lung cancer accounting for the largest SPC burden [23, 25]. We confirmed these findings in the current study and reported novel findings of increasing temporal trends in the risk of head and neck cancer and lung cancer among all cancer survivors during 1980-2009. This finding coincided with the gradual increase of head and neck and chest CT scanning in Tasmania since 1994, and thus may reflect improving detection of SPCs at these sites. In addition, improvement in imaging techniques may have allowed better identification of SPCs that were previously thought to be metastases. It is important to note that in the current study risks of smoking-related SPCs continued to increase and remain high in individuals with a smoking-related first primary cancer. Elevated SPC risks in these survivors might be explained by increased smoking prevalence among these survivors [26]. The decreasing trends of tobacco-related cancer incidence in the general Australian population since the 1980s may also contribute to the increase in SIRs. The decline in expected tobacco-related cancers (the SIR denominator) would lead to a consequent slight increase in relevant SIRs over time [13].

An important finding was the large increase in AERs for prostate cancer among survivors of specific cancer types from 2000 onwards. A recent meta-analysis combining 20 studies reported more frequent screening for breast, cervical, colorectal and prostate cancers among cancer survivors than non-cancer controls. However, all the evidence came from North America and the United Kingdom [11]. In Tasmania, Medicare (Australia's publicly funded universal health care system) records showed a dramatic increase in prostate specific antigen (PSA) tests between 1994 and 2013, from 3,647/100,000 men to 16,572/100,000 respectively

[27]. Thus our findings of increases in AER for prostate cancer among male survivors of head and neck cancer, skin cancer and cancers of the urinary tract may indicate increased screening for prostate cancer among these cancer survivors. The benefits of PSA testing remain controversial given the potential for overdiagnosis of prostate cancer [28].

For all cancer survivors, the risk of a SPC of the prostate was lower than expected in the general population, probably due to the low risk of a second prostate cancer following radical treatment of a first prostate cancer. Prostate cancer survivors accounted for the largest proportion of all cancer survivors in our study but we only observed two second prostate cancer cases among them. In comparison, there were 419.9 cases expected assuming general population incidence rates. After excluding males with a first prostate cancer, the SIR for prostate cancer among all cancer survivors was significantly higher (SIR, 1.16; 95%CI, 1.08-1.25). This finding could also explain the reversal of trend in SIRs for prostate cancer following any first cancer in the multivariable regression model. The SIR values were decreasing over time, whereas the trend in SIRs was increasing over time after adjusting for first cancer types and other patient characteristics including age at first cancer diagnosis and follow-up intervals. We performed additional analyses excluding SPCs occurring in the same site as the first cancer. The SIRs increased from 1.13 (95%CI, 1.03-1.23) with a first cancer diagnosis in 1980-1984 to 1.35 (95%CI, 1.26-1.44) in 2005-2009 (Table 4.8). Although the SIR values increased in each period, the time pattern of SIR values and ratio of SIRs in multivariable Poisson model were almost identical to our main results.

Table 4.8: Temporal trends of standardized incidence ratios (SIRs) for second discordant primary cancers (excluding SPCs occurring in the same site as a first cancer) in Tasmania, 1980-2009.

Calendar periods of first cancer diagnosis	Observed SPCs	Expected SPCs	SIR (95%CI)
1980-1984	512	454	**1.13** (1.03 to 1.23)
1985-1989	695	582	**1.19** (1.11 to 1.29)
1990-1994	997	847	**1.18** (1.11 to 1.25)
1995-1999	1,105	868	**1.27** (1.20 to 1.35)
2000-2004	1,053	766	**1.38** (1.29 to 1.46)
2005-2009	880	653	**1.35** (1.26 to 1.44)
******P* trend			**<0.001**

*P-value was derived from multivariable Poisson regression models with adjustment for sex (not for female organs and prostate), age at first cancer diagnosis, follow-up intervals and first cancer types. Bold numbers indicated statistically significance.

The increasing temporal trend in the risk of colorectal SPCs may reflect increased screening for colorectal cancer among cancer survivors. There was some evidence that cancer survivors were more likely to receive SPC screening if their first cancer was screen-detected [29]. The PSA-testing, national cervical and bowel cancer screening programs were implemented in Australia in 1987, 1991 and 2006 respectively [13]. In the current study, colorectal cancer accounted for the largest AER of SPC among survivors of first cancers of the female organs and prostate during 2000-2009. Intensive screening for colorectal cancer among these cancer survivors may be a possible explanation, especially if their first cancers (cervical cancer or prostate cancer) were screen-detected. Another possible cause is the increased use of abdomen/pelvic CT scan as one of the follow-up procedures for survivors of cancers of the female organs. Alternatively, patients may more actively pursue screening given known benefits. Additional studies are needed to investigate if variations in the mode of second cancer ascertainment explain temporal trends in diagnosis.

Findings from SEER data and Australian data previously observed increasing trends in the overall SPC risks from 1970s and 1980s to 2000 [3, 4]. A recent study of SEER data reported

SPC risk from 1992-2008 but did not assess time patterns and did report SIRs to allow comparisons with previous findings [30]. One Italian study reported nearly constant SIR values in Italy from 1978 to 2010 [5]. However, they did not report change in SIRs with adjustment for patient characteristics (sex, age at first cancer diagnosis, follow-up interval and first cancer type). The association between these patient characteristics and the risk of SPCs has been identified in recent studies [6, 22]. Our study observed an increasing trend in SPC risks from 1980-2000 which was consistent with previous findings in the USA and Australia and reported novel findings of a continued increasing trend in SPC risks from 2000 onwards in multivariable models. The TCR data also has its own advantage due to the relative stable population (less out-migration), therefore less underascertainment of SPCs [16]. However, there were likely to be some SPCs missing from our analysis as a result of migration out of Tasmania to other parts of Australia or beyond. An investigation of data held in the Australian Cancer Database determined that in our study period the proportion of all Tasmanian cancer cases with a subsequent primary cancer registered in another Australian state or territory was very small (0.34%, personal communication).

In summary, the trend in the risk of SPCs among adult-onset cancer survivors has continued to increase over the last three decades. While the patterns of increasing risk were generally consistent with developments in medical imaging and screening programs for some cancer types, the degree to which this explains the increase in SPC risk remains uncertain. The increase in prostate SPC burden among survivors of specific cancer types may reflect active PSA-testing. Patient anxiety, overestimation of the benefits and underestimation of the potential harms of prostate cancer screening could lead to overdiagnosis [12, 28]. Further studies are needed to quantify potential overdiagnosis of SPC among cancer survivors, and thus to assess whether there is potential for optimizing follow-up strategies.

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Chapter 5: Temporal trends in competing mortality from second and subsequent primary cancers, 1980-2014: An Australian population-based study

5.1 Abstract

Background: Subsequent primary cancers (SPCs) compete with first cancers and non-cancer events as the primary cause of death among cancer patients. We aimed to assess temporal trends in SPC mortality since 1980 among adult-onset cancer patients in competing risk models.

Methods: Patients registered with a first cancer in the population-based Tasmanian Cancer Registry, Australia, between 1980-2009 were followed up to December 2014. Cumulative incidence function (CIF) was used to estimate the cumulative incidence of cause-specific deaths in the presence of competing risks. The hazard ratios of SPC-specific deaths were assessed in two regression models: subdistribution hazard ratios from competing risk models (SHRs) and hazard ratios from Cox models (CHRs).

Results: Overall, 5,339 (9.3%) of 57,288 patients developed SPCs and 2,494 died from SPCs during the follow-up. While the cumulative incidence of first cancer deaths at 5, 10, 15 and 20-years gradually decreased over periods of first cancer diagnosis, the cumulative incidence of SPC deaths did not. The SHRs for SPC-specific deaths increased from the reference period 1980-1984 to a peak for first cancers diagnosed in 1995-1999 (SHR=1.18, 95%CI 1.03-1.35), before a decrease in 2005-2009 (SHR=0.82, 95%CI 0.70-0.95) in competing risk models. However, this pattern was not consistent in CHRs. For individuals with specific first cancers,

those with a first prostate cancer in 1995-1999 had the greatest SPC mortality risk (SHR=2.08, 95%CI 1.29-3.36).

Conclusion: Competing risk models, but not Cox models, demonstrated temporal increases in SPC-specific mortality. Greater detection of non-fatal first prostate cancers appears to have contributed to this trend.

5.2 Introduction

Survival for most cancers increased steadily on a global scale from 1995 to 2009 [1]. In Australia, the 5-year relative survival for all cancers increased from 47% in 1982-1987 to 66% in 2006-2010 [2]. For some patients, improved survival after a first cancer diagnosis is offset by risk of death from competing events (i.e. competing mortality) [3]. Events that contribute to competing mortality among cancer patients include those relating to cardiovascular or respiratory complications of cancer treatment, as well as unrelated diseases [4]. Cancer patients are also at risk of competing mortality from subsequent primary cancers (SPCs) [4, 5].

Previous studies have reported risks of SPCs in cancer patients that are greater than expected in the general population [6], as well as a rising incidence of SPCs since 1980 [7-9]. SPCs compete with first cancers and non-cancer events as the cause of death in cancer patients. Although SPCs now occur more frequently, studies of first cancer and SPC-specific mortality in the presence of competing risks are limited in Australia as well as in other parts of the world [10, 11].

Traditional approaches have mostly used the Kaplan-Meier method and Cox proportional hazards models to take into account the time elapsed from onset of first cancer to cause-specific death. However, their consideration of deaths from causes other than the primary interest as 'independent censoring' is biased: a cancer patient who dies from another cause cannot reach the endpoint of interest [3, 12]. The presence of competing events precludes the observation of the endpoint of interest and alters the hazard of its occurrence [13].

Recent studies have emphasised the importance of using competing risk models to estimate cause-specific mortality in studies of cancer, cardiovascular disease and diabetes [3, 11, 13-15]. However, for cancer studies, the focus has generally been on mortality following cancers of specific types and with less than 15 years' surveillance limiting the ability to assess time patterns for competing mortality from SPCs. While our recent study observed an increasing trend in the risk of developing SPCs from 1980-2009, the potential competing mortality from these SPCs was unknown [9]. In the current study, we aimed to assess temporal trends in SPC mortality since 1980 among all adult-onset cancer patients, and patients with specific cancer types, in competing risk models.

5.3 Methods

5.3.1 Study population

We extracted individual data from the population-based Tasmanian Cancer Registry (TCR) in Australia. Individuals registered with a first cancer diagnosis at age 15 years or older between 1980 and 2009 were followed up to December 2014. The study was approved by the Tasmanian Health and Medical Human Research Ethics Committee.

5.3.2 Ascertainment of SPC and deaths

The TCR collected information on new cancer cases and deaths from multiple sources including pathology laboratories, public and private hospitals, radiotherapy centres, and the state's Registrar of Births, Deaths and Marriages. Other state and territory cancer registries routinely notified the TCR of cancer-related deaths occurring outside Tasmania. The TCR coders reviewed death registrations of Tasmanian residents and for causes of death related to a notifiable cancer, coded them using the International Classification of Disease for

Oncology, Third Edition (ICD-O3) for site and morphology. Deaths from other causes were recorded and defined as non-cancer causes. Ascertainment of SPCs followed the International Rules for Multiple Primary Cancers (ICD-O Third Edition). Individuals with a first diagnosis of synchronous primary cancer (cancers diagnosed within 2 months of the first index cancer) were excluded because SPCs in this time frame are more likely to be ascertained as a result of detection bias. Cause-specific deaths were then allocated to three categories:

- Death caused by the first cancer (progression, recurrence or metastasis);
- Death caused by a SPC;
- Non-cancer death.

Cancer cases registered solely on the basis of death certificate notification (diagnosis of cancer at date of death or autopsy) were excluded from the analysis.

5.3.3 Measures of Outcomes

The absolute measure was the cumulative incidence of cause-specific deaths. The relative measure was the hazard ratio of cause-specific deaths.

5.3.4 Statistical analysis

5.3.4.1 Cumulative incidence of cause-specific deaths

Cumulative incidence function (CIF) was used as an alternative to Kaplan-Meier estimates for the cumulative incidence of cause-specific deaths in the presence of competing risks. Kaplan-Meier analysis tends to overestimate cause-specific mortality in cohorts with high competing risks [3]. To illustrate this effect we calculated both Kaplan-Meier estimates and CIF for cumulative incidence of cause-specific deaths (Table 5.3).

5.3.4.2 Mortality risk

The hazard ratios of cause-specific deaths were assessed in two regression models: subdistribution hazard ratios from competing risk models (SHRs) and hazard ratios from Cox models (CHRs). The SHRs evaluate the effect of patient characteristics on cause-specific deaths in the presence of competing risks. When one cause of death is the primary endpoint of interest, patients who die from other causes are still maintained in the risk set. For CHRs of cause-specific deaths, patients who died from causes other than the primary interest are treated as censored events. It is important to note that CHRs describe the effect of covariates on the rate at which events occur in subjects who are currently event-free and SHRs describe the effect of covariates on the rate at which events occur in subjects who are currently event-free or have experienced a competing event [16]. Multivariable models were fitted for the SHRs and CHRs by periods of first cancer diagnosis, adjusting for potential confounders: sex (not for prostate cancer and female breast cancer) and age at first cancer diagnosis. Model diagnostics of plots of Schoenfeld residuals support the assumption of proportional hazard subdistribution in competing risk models and proportional hazards in Cox regression models [17, 18]. Compared to the CHR it is possible that the SHR will be disproportionally affected by the length of follow-up (since subjects do not leave the risk set upon experiencing a competing event), so additional analyses are provided to assess the patterns over decades with follow up time restricted to 5 years.

Subgroup analyses in the cumulative incidence and hazard ratios of cause-specific deaths were conducted for the four most common specific first cancers, and for the first cancer with the highest proportion of SPCs. We also conducted a sensitivity analysis of the trends for all cancers combined after excluding specific cancer patients who presented the highest SPC mortality risk. R project for statistical computing (version 3.3.2, package ‘cmprsk’ and

'survival') were used. A two-sided P value less than 0.05 was considered as denoting statistical significance.

5.4 Results

57,288 individuals were registered with a first primary cancer between January 1980 and December 2009, generating 392,688 person-years at risk at the end of follow-up (December 2014). Median follow-up of the entire cohort was 4.8 years (IQR 0.8-10.5). 5,339 individuals (9.3% of the total sample) developed SPCs. 39,976 (69.8%) individuals died during the follow-up, including 27,140 who died from their first cancer, 2,494 from SPCs and 10,164 from non-cancer causes. The proportion of first cancer deaths gradually decreased with a steady increase in the proportion of SPC deaths and non-cancer deaths from 1980 to 2009 (Figure 5.1). The median age at first cancer diagnosis was 67.0 years (IQR 56.5-75.7). The four most common first cancers in our cohort were colorectal cancer, prostate cancer, female breast cancer and lung cancer. Individuals with a first diagnosis of head and neck cancer had the highest proportion of SPCs (18.3% affected). Therefore, subgroup analyses in the cumulative incidence and hazard ratios of cause-specific deaths were conducted for individuals with a first diagnosis of head and neck cancer, lung cancer, colorectal cancer, female breast cancer and prostate cancer. Table 5.1 shows patient characteristics for those with selected first cancers.

Figure 5.1: Proportion of cause-specific deaths in each calendar year

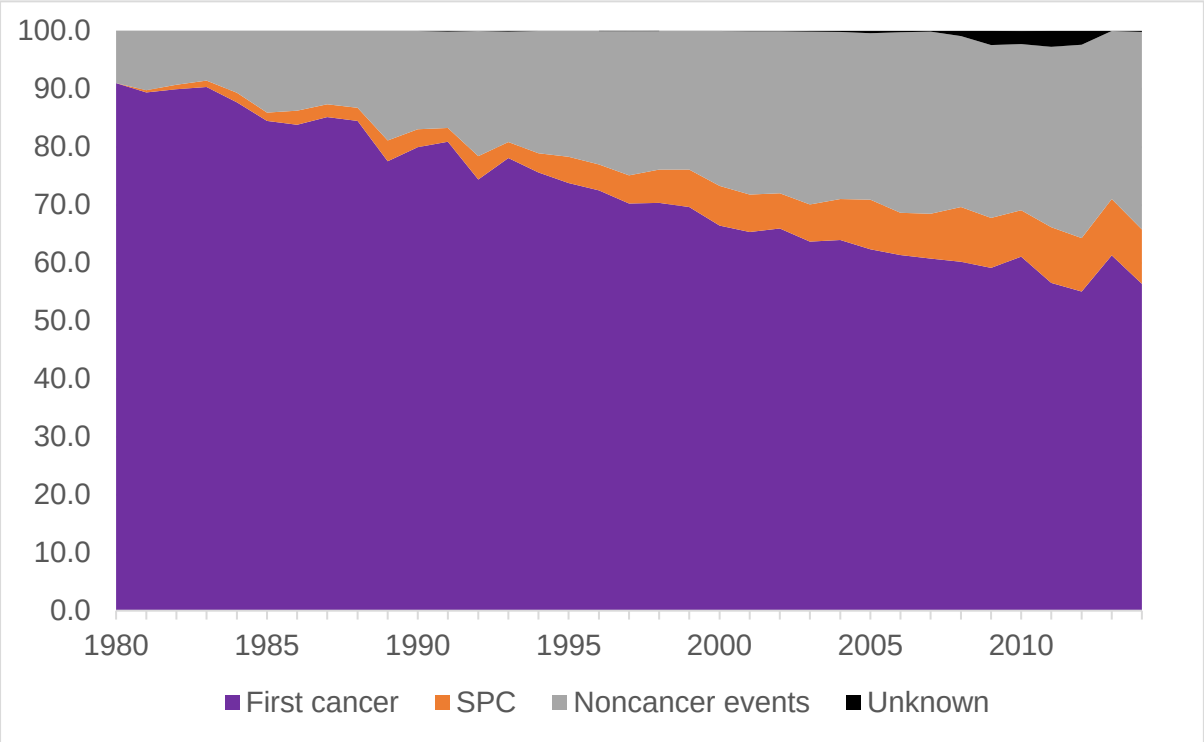

Table 5.1: Characteristics of the study population

First cancer type	No. of patients	No. of patients with SPCs	Median age at first cancer diagnosis, years (IQR)	Median follow-up, years (IQR)	Deaths									
					All causes		First primary		SPC		Non-cancer		unknown	
					No.	(%)	No.	(%)	No.	(%)	No.	(%)	No.	(%)
All types	57,288	5,339	67.0 (56.5-75.7)	4.8 (0.8-10.5)	39,976	(100)	27,140	(67.9)	2,494	(6.2)	10,164	(25.4)	178	(0.5)
Head and neck	2,588	473	63.2 (53.7-72.1)	6.7 (2.0-13.1)	1,752	(100)	802	(45.8)	258	(14.7)	684	(39.0)	8	(0.5)
Lung	6,439	151	68.7 (60.9-75.7)	0.5 (0.2-1.4)	6,257	(100)	5,647	(90.2)	54	(0.9)	552	(8.8)	4	(0.1)
Colorectal	8,246	827	69.1 (60.4-77.4)	3.9 (1.0-9.7)	6,167	(100)	4,093	(66.3)	368	(6.0)	1,682	(27.3)	24	(0.4)
Female breast	6,876	625	59.7 (49.3-70.5)	9.2 (5.2-14.9)	3,461	(100)	1,979	(57.2)	289	(8.3)	1,166	(33.7)	27	(0.8)
Prostate	8,098	986	71.0 (64.4-77.5)	6.6 (3.5-10.1)	4,891	(100)	2,011	(41.1)	514	(10.5)	2,336	(47.8)	30	(0.6)

5.4.1 Cumulative incidence of cause-specific deaths

Overall, the 5-year cumulative incidences of first cancer deaths, SPC deaths and non-cancer deaths were 41.2% (95%CI 40.8-41.6), 1.4% (95%CI 1.3-1.5) and 8.2% (95%CI 7.9-8.4), respectively for individuals with any first cancer diagnosis from 1980-2009 (Figure 5.2). With longer follow-up, the cumulative incidence of first cancer deaths began to plateau while the cumulative incidence of non-cancer and SPC deaths tended to rise steadily (almost linearly). Non-cancer deaths became the leading cause of death at 25 years since first head and neck cancer diagnosis, or at 10 years since first prostate cancer diagnosis.

For individuals with any first cancer type, there was a gradual decrease in the cumulative incidence of first cancer deaths over periods of first cancer diagnoses (Table 5.2). The 5-year cumulative incidence of first cancer deaths decreased from 57.2% (95%CI 55.9-58.4) for cancers diagnosed in 1980-1984 to 30.3% (95%CI 29.6-31.1) in 2005-2009. In contrast, the 5-year cumulative incidence of SPC deaths increased from 1.0% (95%CI 0.8-1.3) for individuals with a first cancer diagnosis in 1980-1984 to a peak of 1.7% (95%CI 1.4-1.9) in 1995-1999, before decreasing to 1.5% (95%CI 1.3-1.7) in 2005-2009. For non-cancer causes, the 5-year cumulative mortality increased from 7.5% (95%CI 6.8-8.1) in 1980-1984 to 9.3% (95%CI 8.7-9.9) in 1990-1994, and then decreased to 7.1%CI (95%CI 6.7-7.6) in 2005-2009. The Kaplan-Meier method overestimated the cumulative incidence of cause-specific deaths at each time interval since first cancer diagnosis (Table 5.3).

For individuals with specific first cancer types, the 5-year cumulative incidence of first cancer deaths steadily decreased from 1980-1984 to 2005-2009 if the first cancer was head and neck, colorectal, female breast or prostate cancer. The cumulative incidence of first cancer deaths remained high across all periods for lung cancer patients. The cumulative

incidence of SPC deaths increased from 1980-1984 to 1995-1999 but fell afterwards for individuals with a first colorectal or prostate cancer. Trends in cumulative incidence of SPC deaths fluctuated over time after a first cancer of the head and neck or female breast. For non-cancer causes, decreasing trends in cumulative mortality were observed only in prostate cancer patients and only for 5 years and 10 years after first diagnosis.

Figure 5.2: Cumulative incidence of cause-specific deaths for all cancer types and five specific cancer types for the whole study period, 1980-2014

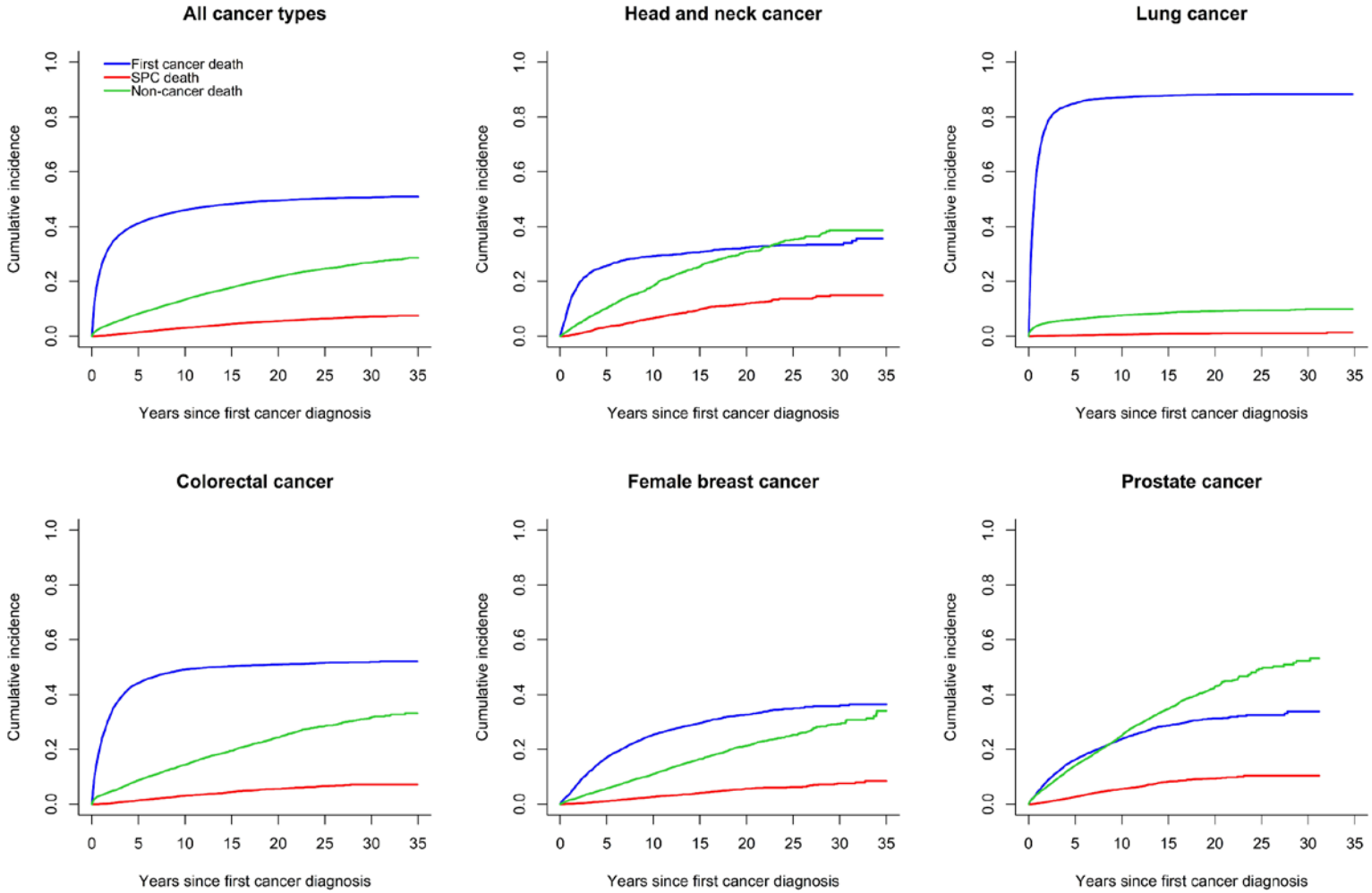

Table 5.2: Cumulative incidence of cause-specific deaths (%) at 5-, 10-, 15- and 20-years after first cancer diagnosis, by periods of first cancer diagnosis, with follow-up to December 2014

	All causes				First primary cancer				Subsequent primary cancer				Non-cancer causes			
	Years after first diagnosis				Years after first diagnosis				Years after first diagnosis				Years after first diagnosis			
	5	10	15	20	5	10	15	20	5	10	15	20	5	10	15	20
All cancer patients																
All periods	50.7	62.4	70.5	76.8	41.1	45.9	48.1	49.3	1.4	3.0	4.4	5.5	8.2	13.3	17.6	21.6
1980-1984	65.6	75.4	81.3	85.2	57.2	61.8	63.8	64.5	1.0	2.1	2.9	3.6	7.5	11.5	14.7	17.1
1985-1989	60.8	70.9	77.4	82.5	51.4	56.3	58.4	59.4	1.1	2.3	3.3	4.2	8.2	12.3	15.7	19.0
1990-1994	54.9	66.0	73.7	79.6	44.3	49.0	51.0	52.0	1.3	2.7	4.1	5.1	9.3	14.4	18.7	22.2
1995-1999	49.9	61.7	69.6		39.9	44.6	46.5		1.7	3.3	4.9		8.4	13.7	17.9	
2000-2004	46.9	58.7			36.5	41.0			1.6	3.3			8.6	14.0		
2005-2009	39.2				30.3				1.5				7.1			
Head and neck cancer patients																
All periods	39.3	54.2	65.9	75.3	25.7	29.2	30.5	32.2	3.4	6.6	9.7	11.9	10.2	18.3	25.4	30.7
1980-1984	45.7	60.6	72.9	81.7	33.4	36.6	38.5	39.4	3.2	6.6	8.5	11.4	9.1	17.4	25.9	30.9
1985-1989	48.1	61.7	69.8	78.3	32.3	36.7	37.8	39.1	3.8	7.1	9.2	10.9	12.0	17.9	22.8	28.3
1990-1994	42.1	57.0	67.8	77.5	26.2	29.6	30.7	32.9	3.3	6.4	8.7	11.1	12.5	21.0	28.4	33.1
1995-1999	37.1	51.2	62.6		22.0	25.3	25.9		3.7	6.7	11.0		11.4	19.2	25.5	
2000-2004	34.6	50.2			20.5	24.0			3.9	6.3			10.2	19.3		
2005-2009	33.1				23.8				2.5				6.7			
Lung cancer patients																
All periods	91.4	95.3	97.3	98.3	84.9	87.1	87.8	88.1	0.3	0.6	0.9	1.0	6.2	7.6	8.5	9.1
1980-1984	93.9	96.4	98.4	98.9	88.2	90.0	90.8	90.9	0.3	0.6	0.7	0.7	5.3	5.8	6.9	7.3
1985-1989	92.0	95.3	97.4	98.4	86.1	88.2	89.1	89.4	0.2	0.2	0.6	0.9	5.6	6.9	7.7	8.1
1990-1994	90.5	94.8	97.0	98.2	83.6	85.8	86.4	86.6	0.5	1.0	1.4	1.4	6.4	8.0	9.2	10.0
1995-1999	92.1	96.0	97.2		86.8	88.7	89.0		0.2	0.5	0.6		5.1	6.9	7.6	
2000-2004	90.4	94.9			81.8	84.1			0.2	0.6			8.4	10.2		
2005-2009	90.3				84.0				0.2				5.8			

Continued	All causes				First primary cancer				Subsequent primary cancer				Non-cancer causes			
	Years after first diagnosis				Years after first diagnosis				Years after first diagnosis				Years after first diagnosis			
	5	10	15	20	5	10	15	20	5	10	15	20	5	10	15	20
Colorectal cancer patients																
All periods	54.3	66.4	74.2	81.0	44.1	49.0	50.2	50.8	1.4	3.0	4.4	5.5	8.7	14.3	19.4	24.2
1980-1984	65.0	75.9	82.3	86.3	57.2	61.8	63.0	63.2	1.0	2.1	3.1	3.8	6.8	12.0	16.1	19.4
1985-1989	62.6	73.8	79.0	85.5	52.6	57.6	58.8	59.2	1.0	2.3	3.1	4.1	9.0	13.9	17.1	22.2
1990-1994	57.3	67.7	75.2	81.1	48.9	52.6	53.5	54.3	1.1	2.8	4.5	5.7	7.2	12.4	17.1	21.0
1995-1999	53.9	66.6	74.8		43.6	48.6	49.5		1.9	4.3	5.8		8.3	13.6	19.1	
2000-2004	52.1	63.3			40.2	44.7			1.7	3.0			10.2	15.4		
2005-2009	43.3				32.1				1.4				9.6			
Female breast cancer patients																
All periods	23.8	39.0	50.2	59.8	16.9	25.2	29.4	32.6	1.1	2.6	4.1	5.6	5.7	10.9	16.4	21.2
1980-1984	43.2	59.0	69.1	76.8	34.2	43.4	48.0	51.1	1.2	2.3	2.9	3.9	7.8	13.4	18.2	21.8
1985-1989	32.8	49.9	61.8	69.0	25.4	35.4	38.7	41.1	0.8	1.9	3.0	4.0	6.6	12.6	20.2	23.9
1990-1994	27.4	42.0	51.8	61.3	19.2	27.5	31.6	34.7	0.9	1.9	2.8	4.3	7.3	12.6	17.5	22.1
1995-1999	21.5	37.5	47.5		14.6	23.7	27.9		1.1	2.5	4.5		5.7	11.2	15.0	
2000-2004	17.3	31.7			11.8	19.2			1.3	3.4			3.8	8.5		
2005-2009	16.4				10.4				1.0				4.8			
Prostate cancer patients																
All periods	32.9	54.3	71.7	83.7	16.1	23.7	28.5	31.1	2.6	5.5	8.2	9.3	14.1	24.9	34.5	42.6
1980-1984	60.4	84.3	93.5	96.3	34.0	45.1	50.0	50.5	1.9	3.5	3.9	4.4	24.5	35.6	39.6	41.4
1985-1989	58.8	81.4	90.7	96.4	35.3	45.7	49.0	50.8	2.0	4.6	5.6	5.8	21.5	31.1	36.1	39.7
1990-1994	46.7	67.3	81.8	89.5	23.6	31.9	36.1	37.6	2.5	4.7	7.0	7.7	20.6	30.6	38.6	43.8
1995-1999	36.7	56.8	71.1		17.0	23.3	26.4		3.7	6.3	8.9		16.0	27.1	35.3	
2000-2004	30.6	49.5			14.1	19.8			2.6	5.2			13.8	24.1		
2005-2009	15.8				6.4				2.4				6.8			

Table 5.3: Kaplan-Meier (KM) estimates and Cumulative Incidence Function (CIF) for cumulative incidence of cause-specific deaths by periods of first cancer diagnosis, with follow-up to December 2014

		All causes				First primary				Subsequent primary				Non-cancer causes			
		Years after first diagnosis				Years after first diagnosis				Years after first diagnosis				Years after first diagnosis			
		5	10	15	20	5	10	15	20	5	10	15	20	5	10	15	20
All cancer patients																	
All period	**KM**	**50.7**	**62.4**	**70.5**	**76.8**	42.7	48.7	52.0	54.1	2.4	6.0	9.9	13.5	11.7	21.6	31.3	40.9
	CIF					41.1	45.9	48.1	49.3	1.4	3.0	4.4	5.5	8.2	13.3	17.6	21.6
1980-1984	**KM**	65.6	75.4	81.3	85.2	59.7	65.5	68.5	69.8	2.2	5.8	9.2	12.9	12.9	24.3	34.8	43.5
	CIF					57.2	61.8	63.8	64.5	1.0	2.1	2.9	3.6	7.5	11.5	14.7	17.1
1985-1989	**KM**	60.8	70.9	77.5	82.6	53.8	59.9	63.0	64.9	2.2	5.8	9.5	13.1	13.2	23.2	32.6	42.8
	CIF					51.4	56.3	58.4	59.4	1.1	2.3	3.3	4.2	8.2	12.3	15.7	19.0
1990-1994	**KM**	54.9	66.1	73.7	79.6	46.3	52.3	55.3	57.3	2.3	5.8	10.0	13.9	14.0	24.5	34.5	43.8
	CIF					44.3	49.0	51.0	52.0	1.3	2.7	4.1	5.1	9.3	14.4	18.7	22.2
1995-1999	**KM**	49.9	61.7	69.6		41.4	47.4	50.2		2.8	6.4	10.7		12.0	22.0	31.1	
	CIF					39.9	44.6	46.5		1.7	3.3	4.9		8.4	13.7	17.9	
2000-2004	**KM**	46.9	58.7			38.1	43.7			2.6	6.1			11.7	21.2		
	CIF					36.5	41.0			1.6	3.3			8.6	14.0		
2005-2009	**KM**	39.2				31.3				2.2				9.2			
	CIF					30.3				1.5				7.1			
Head and neck cancer patients																	
All period	**KM**	**39.3**	**54.2**	**65.9**	**75.3**	26.9	31.6	33.9	37.6	4.7	10.3	17.3	23.3	12.8	25.2	37.4	47.8
	CIF					25.7	29.2	30.5	32.2	3.4	6.6	9.7	11.9	10.2	18.3	25.4	30.7
1980-1984	**KM**	45.7	60.6	72.9	81.7	35.0	39.4	42.6	44.8	4.6	11.6	17.0	26.9	12.5	26.4	43.0	54.6
	CIF					33.4	36.6	38.5	39.4	3.2	6.6	8.5	11.4	9.1	17.4	25.9	30.9
1985-1989	**KM**	48.1	61.7	69.8	78.3	34.3	40.2	42.1	45.2	5.7	12.5	18.0	22.8	16.2	26.8	36.4	48.6
	CIF					32.3	36.7	37.8	39.1	3.8	7.1	9.2	10.9	12.0	17.9	22.8	28.3
1990-1994	**KM**	42.1	57.0	67.8	77.5	27.6	32.1	34.3	39.2	4.6	10.4	15.8	23.1	16.2	29.3	41.9	51.0
	CIF					26.2	29.6	30.7	32.9	3.3	6.4	8.7	11.1	12.5	21.0	28.4	33.1
1995-1999	**KM**	37.1	51.2	62.6		23.1	27.3	28.5		5.0	10.1	18.8		13.9	25.3	35.3	
	CIF					22.0	25.3	25.9		3.7	6.7	11.0		11.4	19.2	25.5	
2000-2004	**KM**	34.6	50.2			21.7	26.1			5.2	9.3			11.8	24.9		
	CIF					20.5	24.0			3.9	6.3			10.2	19.3		
2005-2009	**KM**	33.1				24.6				3.2				8.2			
	CIF					23.8				2.5				6.7			

Continued		All causes				First primary				Subsequent primary				Non-cancer causes			
		Years after first diagnosis				Years after first diagnosis				Years after first diagnosis				Years after first diagnosis			
		5	10	15	20	5	10	15	20	5	10	15	20	5	10	15	20
Lung cancer patients																	
All period	**KM**	**91.4**	**95.3**	**97.3**	**98.3**	89.1	92.1	93.4	94.4	1.6	6.1	14.6	19.0	19.3	35.8	51.1	62.3
	CIF					84.9	87.1	87.8	88.1	0.3	0.6	0.9	1.0	6.2	7.6	8.5	9.1
1980-1984	**KM**	93.9	96.4	98.4	98.9	92.6	94.9	96.1	96.5	2.5	7.3	11.1	11.1	15.1	23.0	54.0	63.9
	CIF					88.2	90.0	90.8	90.9	0.3	0.6	0.7	0.7	5.3	5.8	6.9	7.3
1985-1989	**KM**	92.0	95.3	97.4	98.4	90.0	92.8	94.3	95.1	1.4	1.4	13.9	26.9	18.2	34.8	47.7	56.1
	CIF					86.1	88.2	89.1	89.4	0.2	0.2	0.6	0.9	5.6	6.9	7.7	8.1
1990-1994	**KM**	90.5	94.8	97.0	98.2	87.6	90.7	92.1	92.9	3.5	9.7	18.5	18.5	19.9	37.5	53.4	68.0
	CIF					83.6	85.8	86.4	86.6	0.5	1.0	1.4	1.4	6.4	8.0	9.2	10.0
1995-1999	**KM**	92.1	96.0	97.2		90.2	92.8	93.3		0.4	5.9	11.3		19.5	41.5	52.9	
	CIF					86.8	88.7	89.0		0.2	0.5	0.6		5.1	6.9	7.6	
2000-2004	**KM**	90.4	94.9			87.5	90.8			1.0	6.5			22.3	40.3		
	CIF					81.8	84.1			0.2	0.6			8.4	10.2		
2005-2009	**KM**	90.3				87.9				1.4				18.1	87.9		
	CIF					84.0				0.2				5.8			
Colorectal cancer patients																	
All period	**KM**	**54.3**	**66.4**	**74.2**	**81.0**	46.2	52.4	54.3	55.5	2.5	6.6	10.9	15.2	12.6	24.4	36.3	48.8
	CIF					44.1	49.0	50.2	50.8	1.4	3.0	4.4	5.5	8.7	14.3	19.4	24.2
1980-1984	**KM**	65.0	75.9	82.3	86.3	59.4	65.1	67.1	67.5	2.3	5.8	10.5	13.8	11.8	26.6	39.8	51.2
	CIF					57.2	61.8	63.0	63.2	1.0	2.1	3.1	3.8	6.8	12.0	16.1	19.4
1985-1989	**KM**	62.6	73.8	79.0	85.5	55.6	62.1	63.9	64.8	2.1	6.1	9.4	14.2	13.9	26.2	35.7	51.8
	CIF					52.6	57.6	58.8	59.2	1.0	2.3	3.1	4.1	9.0	13.9	17.1	22.2
1990-1994	**KM**	57.3	67.7	75.2	81.1	51.1	55.5	57.0	58.5	2.0	6.3	12.0	16.4	10.8	22.6	34.5	45.2
	CIF					48.9	52.6	53.5	54.3	1.1	2.8	5.7		7.2	12.4	17.1	21.0
1995-1999	**KM**	53.9	66.6	74.8		45.5	51.9	53.3		3.3	9.1	13.7		12.6	23.6	36.8	
	CIF					43.6	48.6	49.5		1.9	4.3	5.8		8.3	13.6	19.1	
2000-2004	**KM**	52.1	63.3			42.4	48.2			3.1	5.9			14.2	24.3		
	CIF					40.2	44.7			1.7	3.0			10.2	15.4		
2005-2009	**KM**	43.3				33.7				2.1				12.3			
	CIF					32.1				1.4				9.6			

Continued		All causes				First primary				Subsequent primary				Non-cancer causes			
		Years after first diagnosis				Years after first diagnosis				Years after first diagnosis				Years after first diagnosis			
		5	10	15	20	5	10	15	20	5	10	15	20	5	10	15	20
Female breast cancer patients																	
All period	**KM**	**23.8**	**39.0**	**50.2**	**59.8**	17.5	26.9	32.3	36.8	1.3	3.4	6.0	9.1	6.3	13.2	21.4	29.5
	CIF					16.9	25.2	29.4	32.6	1.1	2.6	4.1	5.6	5.7	10.9	16.4	21.2
1980-1984	**KM**	43.2	59.0	69.1	76.8	36.0	47.0	53.5	58.3	1.7	3.8	5.5	9.2	9.8	19.6	29.7	38.7
	CIF					34.2	43.4	48.0	51.1	1.2	2.3	2.9	3.9	7.8	13.4	18.2	21.8
1985-1989	**KM**	32.8	49.9	61.8	69.0	26.5	38.1	42.4	46.2	1.0	2.8	5.4	8.0	7.7	16.8	29.9	37.3
	CIF					25.4	35.4	38.7	41.1	0.8	1.9	3.0	4.0	6.6	12.6	20.2	23.9
1990-1994	**KM**	27.4	42.0	51.8	61.3	20.0	29.6	34.7	39.3	1.1	2.6	4.3	7.7	8.2	15.4	22.9	30.6
	CIF					19.2	27.5	31.6	34.7	0.9	1.9	2.8	4.3	7.3	12.6	17.5	22.1
1995-1999	**KM**	21.5	37.5	47.5		15.2	25.4	30.7		1.3	3.2	6.6		6.2	13.3	18.8	
	CIF					14.6	23.7	27.9		1.1	2.5	4.5		5.7	11.2	15.0	
2000-2004	**KM**	17.3	31.7			12.1	20.3			1.5	4.2			4.1	9.9		
	CIF					11.8	19.2			1.3	3.4			3.8	8.5		
2005-2009	**KM**	16.4				10.7				1.1				5.2			
	CIF					10.4				1.0				4.8			
Prostate cancer patients																	
All period	**KM**	**32.9**	**54.3**	**71.7**	**83.7**	17.6	27.9	36.9	43.8	3.3	8.1	14.8	18.9	15.7	30.8	46.8	63.4
	CIF					16.1	23.7	28.5	31.1	2.6	5.5	8.2	9.3	14.1	24.9	34.5	42.6
1980-1984	**KM**	60.4	84.3	93.5	96.3	42.0	61.7	75.3	77.3	2.8	8.5	14.0	22.5	29.8	55.0	69.4	79.0
	CIF					34.0	45.1	50.0	50.5	1.9	3.5	3.9	4.4	24.5	35.6	39.6	41.4
1985-1989	**KM**	58.8	81.4	90.7	96.4	40.8	59.2	68.5	77.0	3.4	11.2	18.4	20.0	28.0	48.6	63.9	80.2
	CIF					35.3	45.7	49.0	50.8	2.0	4.6	5.6	5.8	21.5	31.1	36.1	39.7
1990-1994	**KM**	46.7	67.3	81.8	89.5	26.8	39.8	48.9	54.1	3.6	8.5	17.1	20.5	24.6	40.6	57.0	70.5
	CIF					23.6	31.9	36.1	37.6	2.5	4.7	7.0	7.7	20.6	30.6	38.6	43.8
1995-1999	**KM**	36.7	56.8	71.1		18.9	27.9	33.9		4.7	9.4	15.8		18.1	33.8	47.3	
	CIF					17.0	23.3	26.4		3.7	6.3	8.9		16.0	27.1	35.3	
2000-2004	**KM**	30.6	49.5			15.3	23.0			3.2	7.3			15.2	28.8		
	CIF					14.1	19.8			2.6	5.2			13.8	24.1		
2005-2009	**KM**	15.8				6.7				2.6				7.1			
	CIF					6.4				2.4				6.8			

5.4.2 Mortality risk

The associations between patient characteristics (sex, age at first cancer diagnosis and period of first cancer diagnosis) and cause-specific deaths were estimated using multivariable competing risk models for SHRs and multivariable Cox regression models for CHRs. For all cancer patients, both SHRs and CHRs of first cancer and non-cancer deaths generally decreased over time, after adjusting for sex (not for female breast cancer and prostate cancer) and age at first cancer diagnosis (Table 5.4). However, the change was not monotonic for SPC deaths. In competing risk models, the risk of SPC deaths increased from 1980-1984 and reached a peak for individuals with a first cancer diagnosis in 1995-1999 (SHR = 1.18, 95%CI 1.03-1.35), before decreasing to 0.82 (95%CI 0.70-0.95) in 2005-2009. However, there was no evidence for a similar pattern in the CHRs of SPC deaths. For the analysis with follow-up restricted to 5 years, the SHRs reflect the effect of periods of first diagnosis on 5-year CIF after adjusting for sex and age at first cancer diagnosis (Table 5.5).

For individuals with specific cancer types (head and neck, lung, colorectal, female breast and prostate), the risk of first cancer and non-cancer deaths generally decreased over time (Table 5.4). The risk of SPC deaths generally decreased over time for head and neck cancer. However, the risk of SPC deaths increased from 1980-1984 (reference) to later periods for individuals with a first diagnosis of colorectal, female breast or prostate cancer in competing risk models. The increase was greatest for individuals with a first diagnosis of prostate cancer in 1995-1999 (SHR = 2.08, 95%CI 1.29-3.36). Individuals with a first colorectal or female breast cancer showed similar patterns of changes in SPC mortality risk but the peak was not statistically significantly greater than the reference period (SHR = 1.35, 95%CI 0.96-1.89 for colorectal and SHR = 1.22, 95%CI 0.81-1.84 for female breast). The peak was delayed to 2000-2004 in female breast cancer. We also conducted a sensitivity analysis of the trends for

all cancers combined after excluding first prostate cancers. The sensitivity analysis showed a lower cumulative incidence of SPC deaths for individuals with a first cancer diagnosis in the 1990s compared with the full analysis, and no evidence for an increase in relevant SHRs.

Table 5.4: The hazard ratios (HRs) of cause-specific deaths by periods of first cancer diagnosis, with adjustment on sex (not for female breast cancer and prostate cancer) and age at first cancer diagnosis

Periods of first cancer diagnosis	All causes	First primary cancer		Subsequent primary cancer		Non-cancer causes	
		SHR	CHR	SHR	CHR	SHR	CHR
	HR (95%CI)	HR (95%CI)	HR (95%CI)	HR (95%CI)	HR (95%CI)	HR (95%CI)	HR (95%CI)
All cancer patients							
1980-1984	1 (ref)	1 (ref)	1 (ref)	1 (ref)	1 (ref)	1 (ref)	1 (ref)
1985-1989	0.88 (0.85-0.91)	0.86 (0.82-0.89)	0.85 (0.82-0.89)	1.08 (0.92-1.25)	0.97 (0.83-1.14)	1.02 (0.95-1.10)	0.93 (0.86-1.00)
1990-1994	0.72 (0.69-0.74)	0.67 (0.65-0.70)	0.66 (0.64-0.69)	1.13 (0.98-1.30)	0.90 (0.77-1.04)	1.06 (0.99-1.14)	0.82 (0.76-0.88)
1995-1999	0.63 (0.61-0.65)	0.59 (0.56-0.61)	0.57 (0.55-0.60)	1.18 (1.03-1.35)	0.93 (0.80-1.08)	0.92 (0.86-0.98)	0.71 (0.66-0.77)
2000-2004	0.57 (0.55-0.59)	0.52 (0.50-0.54)	0.51 (0.49-0.53)	0.97 (0.84-1.12)	0.87 (0.74-1.01)	0.80 (0.75-0.86)	0.68 (0.63-0.73)
2005-2009	0.44 (0.43-0.46)	0.41 (0.39-0.43)	0.40 (0.38-0.42)	0.82 (0.70-0.95)	0.80 (0.67-0.94)	0.56 (0.52-0.61)	0.52 (0.48-0.56)
Head and neck cancer patients							
1980-1984	1 (ref)	1 (ref)	1 (ref)	1 (ref)	1 (ref)	1 (ref)	1 (ref)
1985-1989	0.93 (0.79-1.09)	0.95 (0.75-1.21)	0.98 (0.77-1.24)	0.92 (0.61-1.39)	0.89 (0.59-1.35)	0.91 (0.71-1.17)	0.85 (0.66-1.10)
1990-1994	0.83 (0.71-0.97)	0.76 (0.60-0.97)	0.78 (0.61-0.98)	0.89 (0.60-1.32)	0.85 (0.57-1.29)	0.93 (0.74-1.18)	0.85 (0.67-1.09)
1995-1999	0.71 (0.60-0.83)	0.60 (0.47-0.77)	0.62 (0.49-0.80)	0.94 (0.64-1.39)	0.90 (0.60-1.35)	0.75 (0.59-0.96)	0.72 (0.56-0.93)
2000-2004	0.72 (0.61-0.85)	0.57 (0.45-0.73)	0.60 (0.47-0.77)	0.79 (0.52-1.19)	0.88 (0.57-1.37)	0.73 (0.57-0.94)	0.78 (0.60-1.02)
2005-2009	0.66 (0.55-0.79)	0.65 (0.51-0.83)	0.67 (0.53-0.85)	0.55 (0.33-0.89)	0.78 (0.46-1.32)	0.40 (0.29-0.55)	0.52 (0.37-0.73)
Lung cancer patients							
1980-1984	1 (ref)	1 (ref)	1 (ref)	1 (ref)	1 (ref)	1 (ref)	1 (ref)
1985-1989	0.91 (0.83-1.00)	0.93 (0.84-1.02)	0.90 (0.82-0.99)	1.21 (0.46-3.15)	1.16 (0.42-3.19)	1.14 (0.83-1.57)	1.00 (0.73-1.38)
1990-1994	0.78 (0.71-0.85)	0.80 (0.73-0.89)	0.76 (0.69-0.84)	1.75 (0.71-4.30)	1.12 (0.43-2.92)	1.33 (0.98-1.81)	0.91 (0.67-1.25)
1995-1999	0.78 (0.71-0.85)	0.83 (0.76-0.91)	0.78 (0.71-0.85)	0.79 (0.28-2.24)	0.68 (0.23-2.05)	1.01 (0.73-1.39)	0.81 (0.58-1.12)
2000-2004	0.76 (0.69-0.83)	0.74 (0.67-0.81)	0.72 (0.66-0.79)	1.00 (0.38-2.62)	1.02 (0.36-2.83)	1.37 (1.01-1.85)	1.14 (0.84-1.54)
2005-2009	0.78 (0.71-0.85)	0.82 (0.74-0.90)	0.77 (0.70-0.85)	0.51 (0.16-1.57)	0.72 (0.21-2.48)	0.81 (0.58-1.12)	0.77 (0.55-1.08)

Continued	All causes	First primary cancer		Subsequent primary cancer		Non-cancer causes	
	HR (95%CI)	SHR	CHR	SHR	CHR	SHR	CHR
		HR (95%CI)	HR (95%CI)	HR (95%CI)	HR (95%CI)	HR (95%CI)	HR (95%CI)
Colorectal cancer patients							
1980-1984	1 (ref)	1 (ref)	1 (ref)	1 (ref)	1 (ref)	1 (ref)	1 (ref)
1985-1989	0.92 (0.85-1.01)	0.87 (0.78-0.97)	0.90 (0.80-1.00)	0.97 (0.67-1.42)	0.92 (0.63-1.35)	1.02 (0.87-1.20)	1.00 (0.85-1.19)
1990-1994	0.78 (0.72-0.86)	0.76 (0.68-0.85)	0.76 (0.68-0.84)	1.18 (0.83-1.67)	1.02 (0.71-1.46)	0.89 (0.76-1.05)	0.79 (0.67-0.94)
1995-1999	0.72 (0.66-0.79)	0.66 (0.59-0.74)	0.66 (0.59-0.73)	1.35 (0.96-1.89)	1.19 (0.83-1.71)	0.82 (0.70-0.97)	0.78 (0.66-0.93)
2000-2004	0.66 (0.60-0.72)	0.59 (0.53-0.66)	0.60 (0.54-0.67)	0.76 (0.52-1.12)	0.77 (0.51-1.17)	0.77 (0.65-0.91)	0.81 (0.67-0.96)
2005-2009	0.53 (0.48-0.58)	0.45 (0.40-0.50)	0.45 (0.40-0.50)	0.64 (0.42-0.96)	0.75 (0.48-1.17)	0.68 (0.57-0.81)	0.78 (0.64-0.94)
Female breast cancer patients							
1980-1984	1 (ref)	1 (ref)	1 (ref)	1 (ref)	1 (ref)	1 (ref)	1 (ref)
1985-1989	0.83 (0.74-0.93)	0.75 (0.65-0.87)	0.74 (0.64-0.86)	0.95 (0.60-1.49)	0.89 (0.55-1.42)	1.07 (0.88-1.31)	0.95 (0.78-1.16)
1990-1994	0.66 (0.59-0.74)	0.59 (0.51-0.68)	0.58 (0.50-0.67)	0.96 (0.63-1.47)	0.86 (0.54-1.36)	0.88 (0.73-1.07)	0.75 (0.61-0.91)
1995-1999	0.56 (0.50-0.63)	0.48 (0.42-0.56)	0.47 (0.41-0.55)	1.16 (0.77-1.74)	1.09 (0.70-1.71)	0.71 (0.58-0.87)	0.61 (0.50-0.75)
2000-2004	0.46 (0.40-0.51)	0.37 (0.32-0.43)	0.36 (0.31-0.42)	1.22 (0.81-1.84)	1.29 (0.81-2.04)	0.53 (0.43-0.66)	0.49 (0.39-0.61)
2005-2009	0.40 (0.35-0.46)	0.29 (0.25-0.35)	0.30 (0.25-0.35)	0.94 (0.59-1.52)	1.16 (0.68-1.96)	0.45 (0.35-0.58)	0.53 (0.42-0.68)
Prostate cancer patients							
1980-1984	1 (ref)	1 (ref)	1 (ref)	1 (ref)	1 (ref)	1 (ref)	1 (ref)
1985-1989	0.87 (0.76-0.98)	1.01 (0.85-1.21)	0.92 (0.77-1.10)	1.32 (0.75-2.33)	1.13 (0.64-1.99)	0.84 (0.69-1.02)	0.78 (0.64-0.95)
1990-1994	0.63 (0.56-0.71)	0.65 (0.56-0.77)	0.55 (0.47-0.65)	1.72 (1.05-2.81)	1.11 (0.68-1.82)	0.92 (0.77-1.08)	0.67 (0.57-0.79)
1995-1999	0.47 (0.42-0.53)	0.45 (0.38-0.53)	0.36 (0.30-0.42)	2.08 (1.29-3.36)	1.16 (0.71-1.87)	0.79 (0.67-0.94)	0.52 (0.44-0.62)
2000-2004	0.38 (0.34-0.43)	0.37 (0.31-0.43)	0.29 (0.24-0.34)	1.49 (0.91-2.44)	0.88 (0.54-1.45)	0.64 (0.53-0.76)	0.44 (0.37-0.52)
2005-2009	0.23 (0.21-0.26)	0.19 (0.15-0.22)	0.15 (0.13-0.18)	1.57 (0.96-2.57)	0.92 (0.56-1.51)	0.35 (0.29-0.42)	0.25 (0.21-0.30)

Note: Subdistribution hazard ratios (SHRs) were hazard ratios derived from competing risk models and CHRs were hazard ratios derived from Cox models. Both SHRs and CHRs for cause-specific deaths by calendar periods of first cancer diagnosis (1980-1984, 1985-1989, 1990-1994, 1995-1999, 2000-2004 and 2005-2009) were assessed in multivariable competing risk models and multivariable Cox regression models respectively, with adjustment on sex (not for female organs and prostate) and age at first cancer diagnosis.

Table 5.5: The hazard ratios (HRs) of cause-specific deaths by periods of first cancer diagnosis, with follow-up restricted to 5 years

Periods of first cancer diagnosis	All causes	First primary cancer		Subsequent primary cancer		Non-cancer causes	
	HR (95%CI)	SHR	CHR	SHR	CHR	SHR	CHR
		HR (95%CI)	HR (95%CI)	HR (95%CI)	HR (95%CI)	HR (95%CI)	HR (95%CI)
All cancer patients							
1980-1984	1 (ref)	1 (ref)	1 (ref)	1 (ref)	1 (ref)	1 (ref)	1 (ref)
1985-1989	0.87 (0.83-0.90)	0.85 (0.81-0.89)	0.87 (0.83-0.90)	1.10 (0.79-1.54)	0.98 (0.71-1.37)	1.11 (0.98-1.25)	1.03 (0.91-1.16)
1990-1994	0.69 (0.66-0.72)	0.66 (0.63-0.69)	0.69 (0.66-0.72)	1.22 (0.90-1.66)	0.91 (0.67-1.23)	1.17 (1.04-1.31)	0.94 (0.84-1.06)
1995-1999	0.60 (0.58-0.63)	0.58 (0.55-0.61)	0.60 (0.58-0.63)	1.61 (1.21-2.15)	1.10 (0.82-1.46)	1.05 (0.94-1.18)	0.80 (0.71-0.89)
2000-2004	0.54 (0.52-0.56)	0.51 (0.49-0.54)	0.54 (0.52-0.56)	1.56 (1.17-2.08)	1.00 (0.75-1.33)	1.06 (0.95-1.19)	0.77 (0.69-0.86)
2005-2009	0.42 (0.40-0.44)	0.41 (0.39-0.43)	0.42 (0.40-0.44)	1.42 (1.07-1.88)	0.79 (0.59-1.05)	0.86 (0.77-0.96)	0.57 (0.51-0.64)
Head and neck cancer patients							
1980-1984	1 (ref)	1 (ref)	1 (ref)	1 (ref)	1 (ref)	1 (ref)	1 (ref)
1985-1989	1.10 (0.88-1.37)	0.98 (0.75-1.27)	0.99 (0.76-1.29)	1.22 (0.54-2.75)	1.28 (0.57-2.88)	1.42 (0.89-2.28)	1.41 (0.88-2.25)
1990-1994	0.86 (0.69-1.07)	0.75 (0.57-0.98)	0.75 (0.57-0.97)	1.02 (0.45-2.31)	0.96 (0.43-2.16)	1.35 (0.85-2.13)	1.22 (0.78-1.92)
1995-1999	0.74 (0.59-0.93)	0.61 (0.47-0.81)	0.61 (0.47-0.81)	1.18 (0.54-2.58)	1.06 (0.48-2.31)	1.21 (0.77-1.90)	1.08 (0.69-1.70)
2000-2004	0.68 (0.54-0.84)	0.56 (0.43-0.74)	0.56 (0.43-0.74)	1.29 (0.60-2.77)	1.13 (0.53-2.44)	1.08 (0.68-1.72)	0.95 (0.60-1.50)
2005-2009	0.65 (0.52-0.81)	0.67 (0.52-0.87)	0.65 (0.50-0.85)	0.85 (0.37-1.94)	0.73 (0.32-1.66)	0.71 (0.44-1.17)	0.62 (0.38-1.02)
Lung cancer patients							
1980-1984	1 (ref)	1 (ref)	1 (ref)	1 (ref)	1 (ref)	1 (ref)	1 (ref)
1985-1989	0.91 (0.83-1.00)	0.93 (0.84-1.02)	0.91 (0.82-1.00)	0.58 (0.10-3.48)	0.52 (0.09-3.16)	1.07 (0.73-1.58)	1.00 (0.68-1.47)
1990-1994	0.78 (0.71-0.85)	0.81 (0.73-0.89)	0.77 (0.70-0.84)	1.35 (0.31-5.85)	0.88 (0.21-3.71)	1.17 (0.80-1.71)	0.91 (0.62-1.32)
1995-1999	0.77 (0.71-0.85)	0.83 (0.76-0.92)	0.78 (0.71-0.86)	0.53 (0.09-3.27)	0.33 (0.05-2.01)	0.93 (0.63-1.38)	0.73 (0.49-1.08)
2000-2004	0.75 (0.68-0.82)	0.74 (0.67-0.82)	0.72 (0.66-0.79)	0.44 (0.07-2.90)	0.28 (0.05-1.71)	1.51 (1.06-2.15)	1.15 (0.81-1.63)
2005-2009	0.77 (0.70-0.84)	0.82 (0.74-0.90)	0.77 (0.70-0.85)	0.66 (0.15-2.94)	0.38 (0.07-2.00)	1.03 (0.71-1.50)	0.79 (0.55-1.15)

Continued	All causes	First primary cancer		Subsequent primary cancer		Non-cancer causes	
	HR (95%CI)	SHR	CHR	SHR	CHR	SHR	CHR
		HR (95%CI)	HR (95%CI)	HR (95%CI)	HR (95%CI)	HR (95%CI)	HR (95%CI)
Colorectal cancer patients							
1980-1984	1 (ref)	1 (ref)	1 (ref)	1 (ref)	1 (ref)	1 (ref)	1 (ref)
1985-1989	0.92 (0.83-1.03)	0.86 (0.77-0.97)	0.88 (0.79-0.99)	0.95 (0.41-2.24)	0.92 (0.39-2.16)	1.33 (0.98-1.82)	1.27 (0.93-1.73)
1990-1994	0.79 (0.71-0.88)	0.77 (0.69-0.86)	0.77 (0.69-0.86)	1.10 (0.50-2.46)	0.95 (0.42-2.11)	1.06 (0.77-1.45)	0.94 (0.69-1.29)
1995-1999	0.68 (0.62-0.76)	0.65 (0.58-0.73)	0.64 (0.57-0.72)	1.88 (0.92-3.87)	1.45 (0.70-2.98)	1.14 (0.84-1.53)	0.93 (0.69-1.26)
2000-2004	0.65 (0.59-0.72)	0.58 (0.52-0.66)	0.59 (0.52-0.66)	1.66 (0.80-3.44)	1.25 (0.60-2.59)	1.37 (1.03-1.82)	1.10 (0.82-1.46)
2005-2009	0.49 (0.45-0.55)	0.43 (0.39-0.49)	0.43 (0.38-0.48)	1.31 (0.63-2.72)	0.86 (0.41-1.80)	1.30 (0.98-1.72)	0.92 (0.69-1.22)
Female breast cancer patients							
1980-1984	1 (ref)	1 (ref)	1 (ref)	1 (ref)	1 (ref)	1 (ref)	1 (ref)
1985-1989	0.75 (0.63-0.88)	0.71 (0.59-0.86)	0.71 (0.59-0.86)	0.63 (0.22-1.83)	0.59 (0.20-1.70)	0.92 (0.62-1.37)	0.91 (0.62-1.33)
1990-1994	0.61 (0.52-0.72)	0.53 (0.44-0.63)	0.53 (0.44-0.63)	0.76 (0.30-1.94)	0.69 (0.27-1.76)	1.01 (0.71-1.46)	0.98 (0.69-1.38)
1995-1999	0.46 (0.39-0.54)	0.39 (0.32-0.48)	0.39 (0.32-0.47)	0.99 (0.41-2.39)	0.83 (0.35-1.99)	0.84 (0.58-1.22)	0.74 (0.52-1.06)
2000-2004	0.36 (0.30-0.42)	0.31 (0.26-0.38)	0.30 (0.25-0.37)	1.15 (0.50-2.66)	0.93 (0.41-2.11)	0.56 (0.38-0.82)	0.48 (0.33-0.69)
2005-2009	0.34 (0.29-0.40)	0.27 (0.22-0.33)	0.26 (0.22-0.32)	0.90 (0.38-2.15)	0.73 (0.31-1.71)	0.68 (0.47-0.98)	0.61 (0.43-0.87)
Prostate cancer patients							
1980-1984	1 (ref)	1 (ref)	1 (ref)	1 (ref)	1 (ref)	1 (ref)	1 (ref)
1985-1989	0.92 (0.78-1.08)	0.99 (0.80-1.22)	0.92 (0.77-1.10)	1.05 (0.42-2.61)	1.00 (0.40-2.48)	0.81 (0.62-1.07)	0.82 (0.63-1.07)
1990-1994	0.67 (0.58-0.77)	0.60 (0.49-0.73)	0.55 (0.47-0.65)	1.38 (0.64-2.99)	1.15 (0.53-2.48)	0.80 (0.63-1.02)	0.73 (0.58-0.91)
1995-1999	0.49 (0.43-0.57)	0.41 (0.33-0.50)	0.36 (0.30-0.42)	2.07 (0.98-4.35)	1.54 (0.73-3.23)	0.64 (0.50-0.82)	0.53 (0.42-0.67)
2000-2004	0.39 (0.34-0.45)	0.32 (0.26-0.39)	0.29 (0.24-0.34)	1.52 (0.71-3.23)	1.06 (0.50-2.27)	0.55 (0.43-0.69)	0.44 (0.35-0.55)
2005-2009	0.21 (0.18-0.24)	0.15 (0.12-0.18)	0.15 (0.13-0.18)	1.47 (0.70-3.08)	0.93 (0.45-1.95)	0.30 (0.23-0.39)	0.23 (0.18-0.29)

Note: Subdistribution hazard ratios (SHRs) were hazard ratios derived from competing risk models and CHRs were hazard ratios derived from Cox models. Both SHRs and CHRs for cause-specific deaths by calendar periods of first cancer diagnosis (1980-1984, 1985-1989, 1990-1994, 1995-1999, 2000-2004 and 2005-2009) were assessed in multivariable competing risk models and multivariable Cox regression models respectively, with adjustment on sex (not for female organs and prostate) and age at first cancer diagnosis.

5.5 Discussion

An aging population, greater uptake of cancer screening and the development of advanced imaging techniques has led to more frequent occurrence of SPCs among adult-onset cancer survivors and the possibility of competing mortality risk associated with them [9]. In the current study, we found that the risk of first cancer deaths gradually decreased from 1980-2009. In contrast, the risk of SPC deaths increased to a peak for individuals with a first cancer diagnosis in the late 1990s, then fell to a risk below that of the early 1980s in competing risk models. For individuals with specific cancers, the SPC mortality risk was greatest in individuals with a first diagnosis of prostate cancer in the late 1990s and the risk remained higher during 2000-2009 than in the early 1980s.

A recent study reported the risk of cause-specific deaths in cancer patients using the proportion of deaths due to each cause [19]. It concluded that there was a higher risk of non-cancer death than cancer deaths in recent years. However, temporal trends in proportions of cause-specific deaths could be influenced by the follow-up time. Specifically, the longer the follow-up, the more likely deaths due to non-cancer causes will be observed. This is reflected in our study results with a steady increase in the proportion of non-cancer deaths from 1980 to 2009 (Figure 5.1). However, in the competing risk models we showed that the risk of non-cancer deaths was significantly lower for first cancers diagnosed in 2005-2009 than in the reference period 1980-1984. Thus, when accounting for follow-up time and the presence of competing causes of death, we no longer have evidence for an increase in the risk of non-cancer deaths over time.

The competing risk approach is a more advanced method for estimating a patient's outcome beyond that achievable with traditional methods, especially for cancer patients who are at risk

of first cancer deaths as well as competing mortality from SPCs and non-cancer causes [11]. Recent studies have reported competing mortality among individuals with specific cancers in one period (e.g. head and neck cancer, colorectal cancer, breast cancer and prostate cancer) [10, 11, 20-22]. The current study is novel in that it identified temporal trends in first cancer, SPC-specific and non-cancer causes mortality among individuals with all cancer types from 1980-2009. The gradual decrease in the risk of first cancer deaths could be due to early detection of first cancers through improved screening and diagnostic techniques, and advances in curative therapy [23]. It could also be a result of increased detection of nonfatal first cancers which have low mortality rates [24].

The most novel finding in our study is the increased cumulative mortality and mortality risk due to SPCs for patients with a first cancer diagnosis in the 1990s. The increase was largely influenced by first diagnoses of prostate cancer in the 1990s, confirmed through a sensitivity analysis of the trends for all cancers combined after excluding first prostate cancers. One possible explanation of this finding is increased detection of nonfatal first cancers of the prostate and subsequent registration of more lethal cancers as SPCs. The increase in diagnosis of prostate cancer coincides with the listing of prostate-specific antigen (PSA) testing on the Australian Medicare Benefits Schedule (a publicly funded universal health care system in Australia) in 1989 [25]. The incidence of prostate cancer in Australia maintained at around 82 new cases per 100,000 males between 1982 to 1988, followed by a rapid increase to 184 per 100,000 in 1994, a sharp decline to 130 per 100,000 in 1997, and then steady again until a gradual increase from 2002 to 2009 [26]. Prostate cancer incidence in Tasmania has the same pattern as the national statistics (data not shown). Individuals who had a prostate cancer diagnosis in the 1990s were more likely to die from their SPCs compared to any other periods during 1980-2009. This suggests that some prostate cancers identified in the peak PSA-

testing era of the 1990s may have been of less clinical significance, and were potentially "overdiagnosed" [24, 27]. The increase in SPC mortality risk may also be related to the decline in prostate cancer mortality. Improved treatment for prostate cancer has prolonged overall survival for prostate cancer patients [28, 29] providing the opportunity for SPCs to develop and cause death as a competing event.

Although individuals with a first diagnosis of head and neck cancer had the highest proportion of SPCs, we did not observe an apparent trend in SPC mortality risk over periods of first cancer diagnosis. The most frequent SPC among head and neck cancer patients was lung cancer, which was likely to be smoking-related. Secondary prevention of cigarette smoking among these patients may help to reduce the development of smoking-related SPCs.

Another possible contributor to the increased mortality risk due to SPCs could be the development of more lethal treatment-related SPCs as a result of aggressive treatment of first cancers [30]. For individuals diagnosed with prostate cancer in 1995-1999, deaths due to colorectal cancer accounted for the second biggest proportion in SPC deaths. A recent meta-analysis of 21 studies confirmed a higher risk of colorectal cancer following radiotherapy for prostate cancer [31]. The role of radiotherapy or chemotherapy in the development of treatment-related SPCs has also been identified with other first cancer sites [32-34]. In our study, the risk of SPC deaths increased for females with breast cancer in 2000-2004 but the increase did not reach statistical significance. An increased number of deaths due to haematological malignancies may be related to breast cancer treatment [35].

The greatest strength of our study was the application of the competing risk approach in a population-based sample to identify patterns of cause-specific mortality among patients with all cancer types and specific cancer types. The competing risk method calculated the "real"

probability of cause-specific deaths where individuals are at risk of death from more than one cause. Previous studies used standardized mortality ratios (SMRs) for cause-specific mortality among cancer patients [19, 36, 37]. However, derivation of SMRs for first cancers deaths is inappropriate because expected mortality due to first cancer in the general population (unaffected by cancer) is zero and internal comparisons between first cancer mortality and other causes of mortality are not possible [36-38]. Finally, the TCR data is comprehensive due to the full coverage of the whole state, which has a relatively stable population. This study also has some potential limitations. First, the TCR was established in 1978. Some cancers classified as a "first diagnosis" in the early 1980s might be SPCs, thus resulting in miscoding of first cancer deaths in the early 1980s. Second, a lack of treatment data in the TCR records precluded evaluation of different treatment regimens on patients' outcome.

In conclusion, our study observed an increased risk of SPC deaths for individuals with a first cancer diagnosis in the 1990s, while the risk of first cancer and non-cancer deaths generally decreased from 1980-2009. The increased risk of SPC deaths in the 1990s possibly reflects greater detection of some non-fatal cancers that were registered as first cancers, or the adverse late effects of cancer treatment. Wider application of competing risk analysis in studies of mortality after cancer may help to alert clinicians, policy-makers and patients to changes in the detection of non-fatal first cancers or the prognosis of SPCs.

5.6 References

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Chapter 6: Cardiovascular and other competing causes of death among cancer patients, 2006-2015: An Australian population-based study

6.1 Abstract

Background: With improved cancer survivorship, cardiovascular disease (CVD) and other non-cancer events compete with cancer as the underlying cause of death but mortality risks in competing risk settings have not been well characterized.

Methods: We identified 21,637 individuals with a first cancer registered between 2006-2013, with follow-up to 2015, in the population-based Tasmanian Cancer Registry, Australia. Cumulative incidences of deaths due to specific competing events were assessed in competing risk settings. Standardized mortality ratios (SMRs) and absolute excess risks (AERs) for non-cancer deaths were calculated for comparison with the general population.

Results: Overall, 8,844 deaths were observed with 1,946 (22.0%) from competing events. The cumulative incidence of CVD deaths increased significantly with age at first cancer diagnosis and exceeded other competing events at age 65 years or older. The risk of CVD deaths was more common than expected in the first follow-up year (SMR, 1.44; 95%CI 1.26-1.64; AER, 36.8/10,000 person-years). The SMR and AER for CVD deaths varied by first cancer site showing increased risks after a first diagnosis of lung cancer, haematological malignancies and urinary tract cancers. For other non-cancer events, the SMRs significantly increased for infectious disease and respiratory disease and were highest in the first follow-up year.

Conclusion: CVD was the leading cause of competing mortality among Tasmanian cancer patients diagnosed from 2006-2013. The higher than expected occurrence of death due to CVD and other non-cancer events during the first year after a cancer diagnosis highlights the importance of early preventive interventions.

Key words: cancer, non-cancer mortality, cardiovascular mortality, competing risk, population-based.

6.2 Introduction

The number of people living with a history of cancer has continued to increase over recent decades in most developed countries [1]. In 2012, nearly one million Australians were living with a history of cancer diagnosed since 1982, and in 2016, more than 15.5 million Americans had a history of cancer [2]. With successful cancer treatment, patients are less likely to die from cancer and cancer mortality rates have continued to fall [2, 3]. Patients are also more likely to live with cancers that are not life-threatening because more sensitive screening tests have increased the chance of detecting slow- or non-progressive cancers [4].

Previous studies suggest that non-cancer events are playing an important role as the cause of death among individuals with specific cancers [5-8] and among patients with all types of cancers combined [9, 10]. Patients may experience devastating non-cancer events related to their cancer treatment (e.g. chemotherapy–related cardiac dysfunction) or as a result of a deterioration of pre-existing or new non-cancer disease [11].

Cardiovascular disease (CVD) was the leading cause of death worldwide from 2006-2016 [12] and a number of studies have assessed CVD mortality in cancer survivors [13-17]. However, studies of mortality due to other non-cancer events are outdated [9] or only report on death due to specific causes such as suicide [14, 15] and respiratory disease [7, 17]. To the best of our knowledge, only one recent study from the United States reported the risk of death due to specific non-cancer events among patients with all cancers combined [10]. However, it did not consider follow-up time nor the presence of competing risks, which may have biased the comparison of cancer mortality with non-cancer mortality within the cohort. Our previous study identified an increasing risk of death from non-cancer events among cancer patients with longer survival time but data on specific non-cancer events was limited [18]. This study

aimed to assess specific non-cancer mortality among all individuals with a cancer diagnosis in Tasmania over an 8-year period in the presence of competing risks. We also compared the risk of death due to specific non-cancer events with that expected in the general population.

6.3 Methods

6.3.1 Study population

We identified individuals registered with a first cancer diagnosed at age 15 years or older in the Tasmanian Cancer Registry (TCR), Australia, between January 2006 and December 2013. Follow-up of the cohort ended on December 31, 2015. The TCR was established in 1977 as a population-based registry covering the entire state. We obtained ethics approval for the study from the Tasmanian Health and Medical Human Research Ethics Committee.

6.3.2 Ascertainment of cause of death

The TCR routinely received notifications of deaths from the Tasmanian Registry of Births, Deaths and Marriages. Each death subsequently recorded in the TCR dataset included up to five causes of death, up to eight antecedent causes of death and up to two other significant conditions noted at time of death. The TCR's coders determined whether the cause of death was related to a notifiable cancer and coded it using International Classification of Diseases for Oncology, Third Edition (ICD-O3) codes. Deaths from non-cancer causes were all given a single non-cancer code. To obtain the specific cause of death due to non-cancer causes, the TCR database was linked to the national Cause of Death Unit Record File (COD-URF). The COD-URF is a dataset including information on causes of death relating to all deaths registered in Australia. The Australian Bureau of Statistics (ABS) codes and categorizes the

underlying cause of death and other contributing causes using the 10th revision of the International Classification of Diseases (ICD-10) coding rules.

We compared the records of the underlying cause of death in the TCR dataset with the COD-URF. If there were any differences between the recorded causes between the two sources, we reviewed the details in the death records, and where possible the digital medical records stored in the public hospital system, and then assigned the underlying cause of death in consultation with a medical advisor and experienced cancer coder.

Underlying causes of death due to cancer were classified as causes due to the first recorded primary cancer or, if applicable, a subsequent primary cancer (SPC). Underlying causes of death due to non-cancer causes were grouped according to the ICD-10 classification of disease. Deaths due to non-cancer causes were then allocated to one of nine categories by ICD-10 code: deaths due to infectious disease (A00-B99), endocrine, nutritional and metabolic diseases (E00-E90), mental and behavioural disorders (F00-F99), disease of the nervous system (G00-G99), CVD (I00-I99), respiratory disease (J00-J99), digestive disease (K00-K93), genitourinary disease (N00-N99) and other non-cancer events (D50-D89, H00-H95, L00-L99, M00-M99, O00-O99, P00-P99, Q00-Q99, R00-R99, S00-T98, V01-Y98, Z00-Z99, U00-U89). Patients without a death record before the end of follow-up (December 2015) were deemed to be still living.

6.3.3 Statistical analysis

6.3.3.1 Internal comparison within the cohort

The cumulative incidence function (CIF) was used to estimate deaths due to non-cancer events in the presence of competing risks [19]. This is preferred to the traditional Kaplan-Meier

method which usually overestimates the absolute risk in cause-specific survival [20]. Estimates for cumulative incidence of death at 1-, 5-, and 9-years post primary cancer diagnosis were presented by sex, age grouping (15-64, 65-74, 75-84 and ≥85 years), and first cancer type.

6.3.3.2 Comparison with the general population

Standardized mortality ratios (SMRs) and absolute excess risks (AERs) were computed for each underlying cause of death due to non-cancer events using the standard person-years approach [21, 22]. Person-years at risk (PYR) started at the date of the first cancer diagnosis and ended at the date of death, or the end of follow-up (December 31, 2015), whichever came first. The SMR was calculated as the ratio of observed to expected deaths. Expected deaths were calculated using PYR for all specific sex, 5-year age group and 1-year calendar period strata multiplied by the corresponding mortality rate for the Tasmanian population. The AER was calculated by subtracting the expected number of deaths from the observed number and then dividing by 10,000 person-years. The SMRs and AERs for each non-cancer event were then stratified by sex, age at first cancer diagnosis (15-64, 65-74, 75-84 and ≥85 years), follow-up interval (<1 year, 1-4 years, 5-9 years) and first cancer type. The 95% confidence intervals (CIs) of the SMRs and AERs were derived from Poisson regression models. Statistical analyses were conducted using R project for statistical computing (version 3.3.2, package 'cmprsk' and 'survival') and Stata software (version 15; StataCorp LLC, College Station, Texas).

6.4 Results

Overall, 8,844 deaths were observed among 21,637 eligible cancer patients who accumulated 88,722 PYR during 2006-2015. There was a 4.2% discrepancy (352 of a total 8,844 death

records) between the TCR recorded cause of death and the COD-URF due to differences between the TCR and ABS cause of death coding guidelines. 174 deaths were registered as non-cancer causes in the TCR but as cancer causes in the COD-URF, and 178 deaths were registered as cancer causes in the TCR but non-cancer causes in the COD-URF. Following review, 127 of the 352 underlying causes of death were assigned using ABS codes and the remainder had a TCR allocated code.

Patient characteristics are presented in Table 6.1. Underlying causes of death were ascertained among 8,756 of 8,844 deaths (99.0 %). There were 1,946 deaths due to competing events (332 from SPCs, 741 from CVD and 873 from other non-cancer events). The mean age of patients at the first cancer diagnosis was 65.8 years (median 66.5 years; 25th-75th percentiles, 57.4-75.7 years). The mean follow-up was 4.1 years (median 3.8 years; 25th-75th percentiles, 1.6-6.5 years). According to absolute numbers, the most common cause of non-cancer deaths was CVD (n=741), followed by respiratory disease (n=271), endocrine, nutritional and metabolic diseases (n=124) and mental and behavioural disorders (n=111) (Table 6.2).

Table 6.1: Characteristics of the patients

Characteristic	Patients	
	No.	(%)
Overall	21,637	(100.0)
Sex		
Male	12,156	(56.2)
Female	9,481	(43.8)
Age at diagnosis		
15-64	9,790	(45.2)
65-74	6,065	(28.0)
75-84	4,274	(19.8)
85+	1,508	(7.0)
Follow-up intervals		
< 1 y	4,437	(20.5)
1-4 y	8,907	(41.2)
5-9 y	8,293	(38.3)
First cancer sites		
Head and neck	892	(4.1)
Digestive, except colorectal	1,605	(7.4)
Colorectal	3,102	(14.3)
Lung	2,050	(9.5)
Hematological	1,006	(4.7)
Skin	2,196	(10.2)
Breast	2,649	(12.2)
Female organs	843	(3.9)
Prostate	3,967	(18.3)
Urinary tract	1,164	(5.4)
Lymphoma	668	(3.1)
Others	1,495	(6.9)

Table 6.2: Characteristics of non-cancer deaths among cancer patients during 2006-2015

	CVD*	Infection	Endocrine	Mental	Nervous	Respiratory	Digestive	Genitourinary	Others	Total
Overall	741	39	111	124	62	271	79	52	135	1,614
Sex										
Male	447	27	65	67	35	168	44	34	90	977
Female	294	12	46	57	27	103	35	18	45	637
Age at diagnosis										
15-64	74	10	12	5	9	30	21	2	31	194
65-74	160	6	34	14	14	76	13	9	34	360
75-84	302	16	49	58	25	111	27	21	42	651
85+	205	7	16	47	14	54	18	20	28	409
Follow-up intervals										
< 1 y	228	15	36	15	11	69	24	14	37	449
1-4 y	354	15	55	74	34	144	38	29	64	807
5-9 y	159	9	20	35	17	58	17	9	34	358
First cancer sites										
Head and neck	30	1	2	8	3	14	8	0	11	77
Digestive, except colorectal	28	4	3	4	1	9	8	5	4	66
Colorectal	151	8	26	20	8	40	16	4	19	292
Lung	48	3	6	0	2	40	3	3	11	116
Haematological	53	2	8	6	3	25	2	8	12	119
skin	78	4	12	26	10	23	4	5	15	177
Breast	61	2	9	16	11	20	6	3	11	139
Female organs	13	2	5	2	1	4	8	1	2	38
Prostate	161	6	20	28	13	54	14	13	30	339
Urinary tract	71	5	9	8	6	21	6	6	10	142
Lymphoma	21	1	7	4	3	10	2	3	7	58
Others	26	1	4	2	1	11	2	1	3	51

*CVD: Cardiovascular disease.

6.4.1 Cumulative incidence of cause-specific deaths

For individuals with all cancers combined, CVD was the leading cause of competing mortality in both male and female cancer patients (Figure 6.1). The cumulative incidence of deaths due to CVD exceeded other competing events for those first diagnosed with cancer at age 65 years or older and was greatest for individuals with a first cancer diagnosis at age 85 or above (Figure 6.2). The 5-year cumulative incidence of deaths due to CVD increased from 0.7% at age 15-64y to 2.1% at age 65-74y, 6.0% at age 75-84y and 13.1% at age 85 or older respectively (Table 6.3). For all causes of death, first cancer was the leading cause of death among individuals with a cancer diagnosis between 2006-2013 (Figure 6.3).

Table 6.3 also illustrates the cumulative incidence of deaths due to all non-cancer events and specific non-cancer events by first cancer types. Individuals whose first cancer was a haematological malignancy had a higher 1-year cumulative incidence of non-cancer deaths than those with other first cancer types. At 5 years and 9 years following a first diagnosis, individuals with a first cancer of the urinary tract were more likely to experience non-cancer deaths compared to other cancer types.

The 1-year cumulative incidence of CVD deaths was greatest among patients whose first cancer was a haematological malignancy (1.9%). The 5-year and 9-year cumulative incidence of CVD deaths were highest among patients with a first cancer of the urinary tract (5.9% and 8.1%, respectively). The cumulative incidences of other non-cancer events were consistently lower than for CVD.

Figure 6.1: Cumulative incidence function curves for deaths due to subsequent primary cancers (SPCs) and non-cancer events by sex.

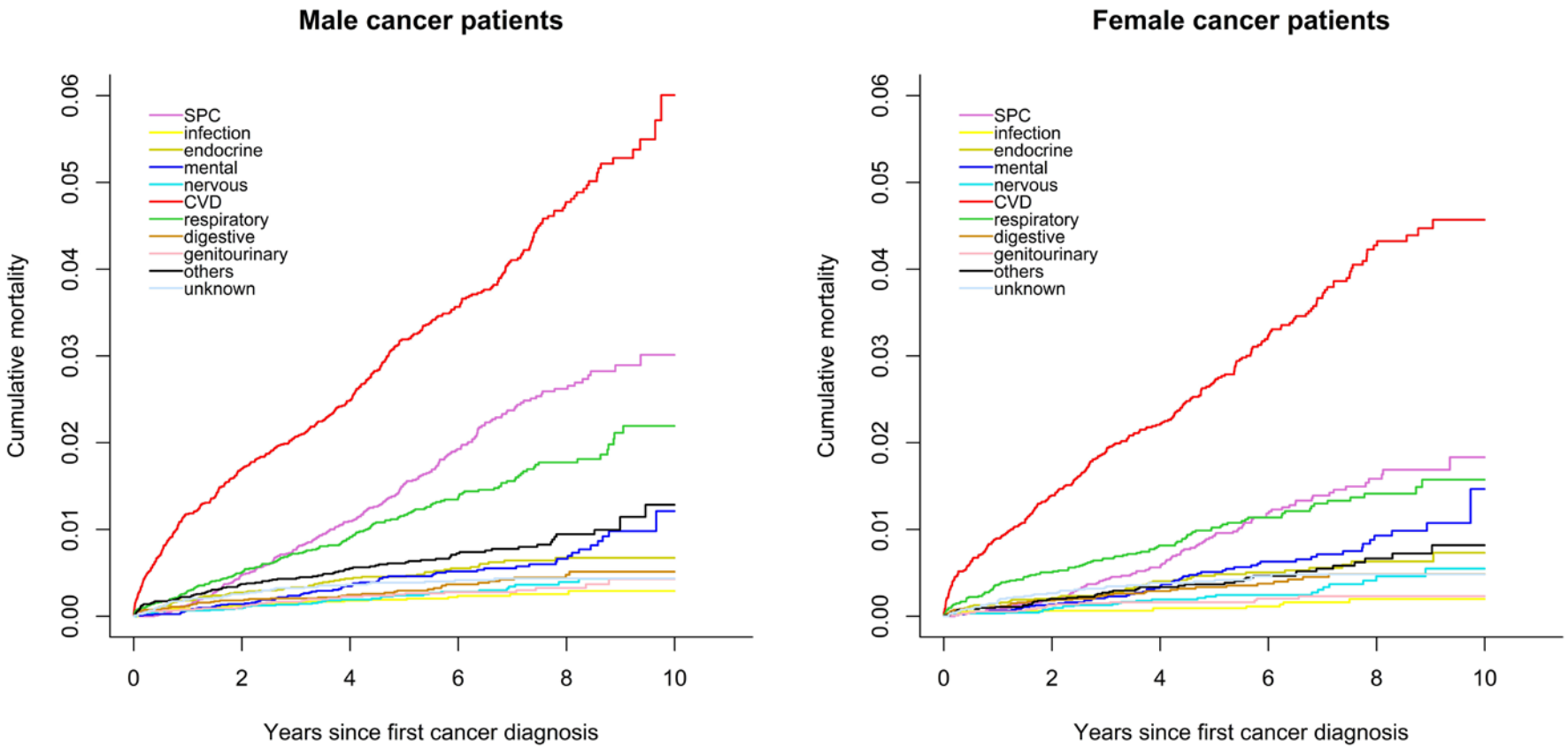


Figure 6.2: Cumulative incidence function curves for deaths due to subsequent primary cancers (SPCs) and non-cancer events by age at first cancer diagnosis.

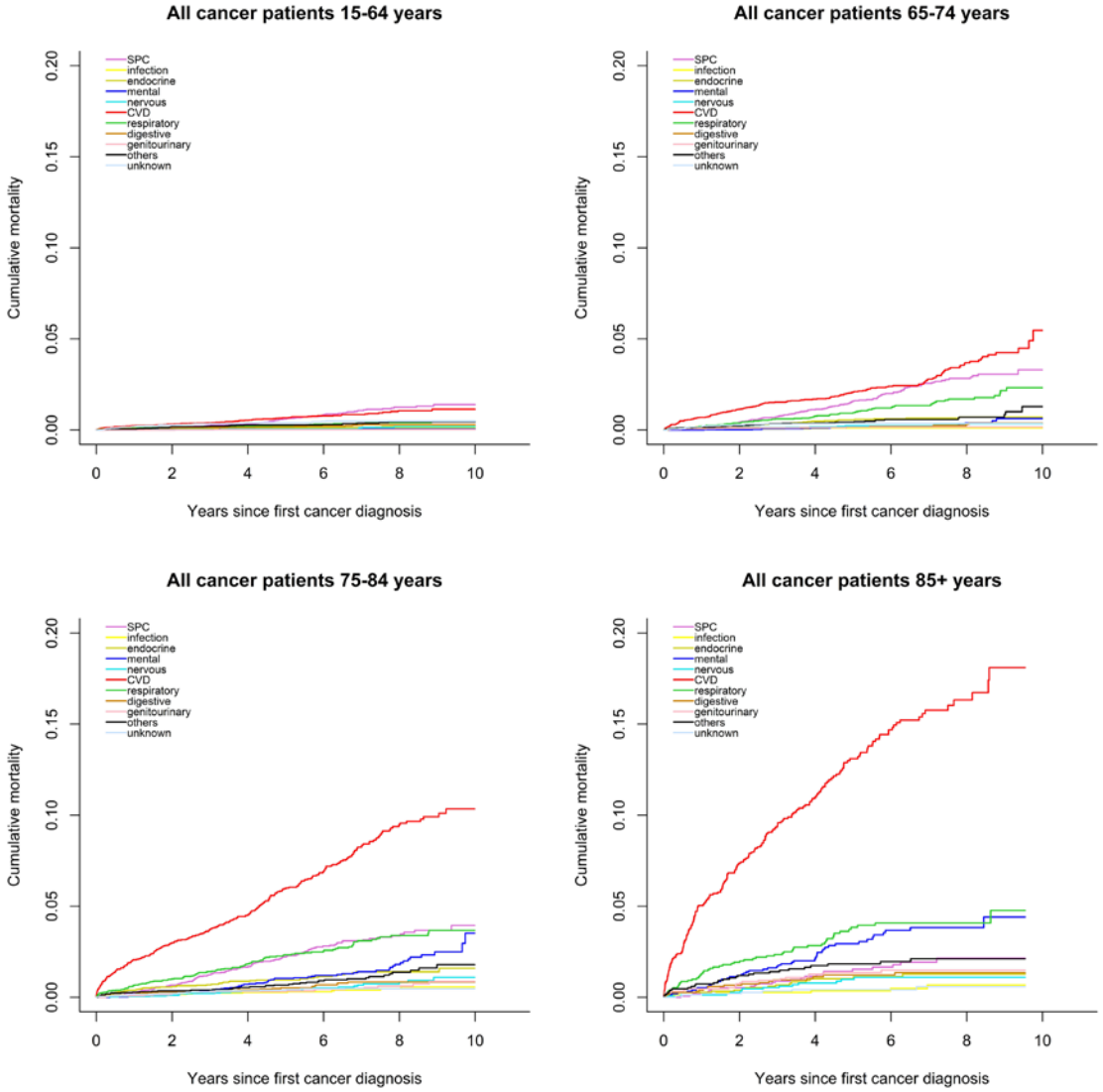


Table 6.3: Cumulative incidence (%) of death due to non-cancer events, by sex, age at first cancer diagnosis and first cancer sites

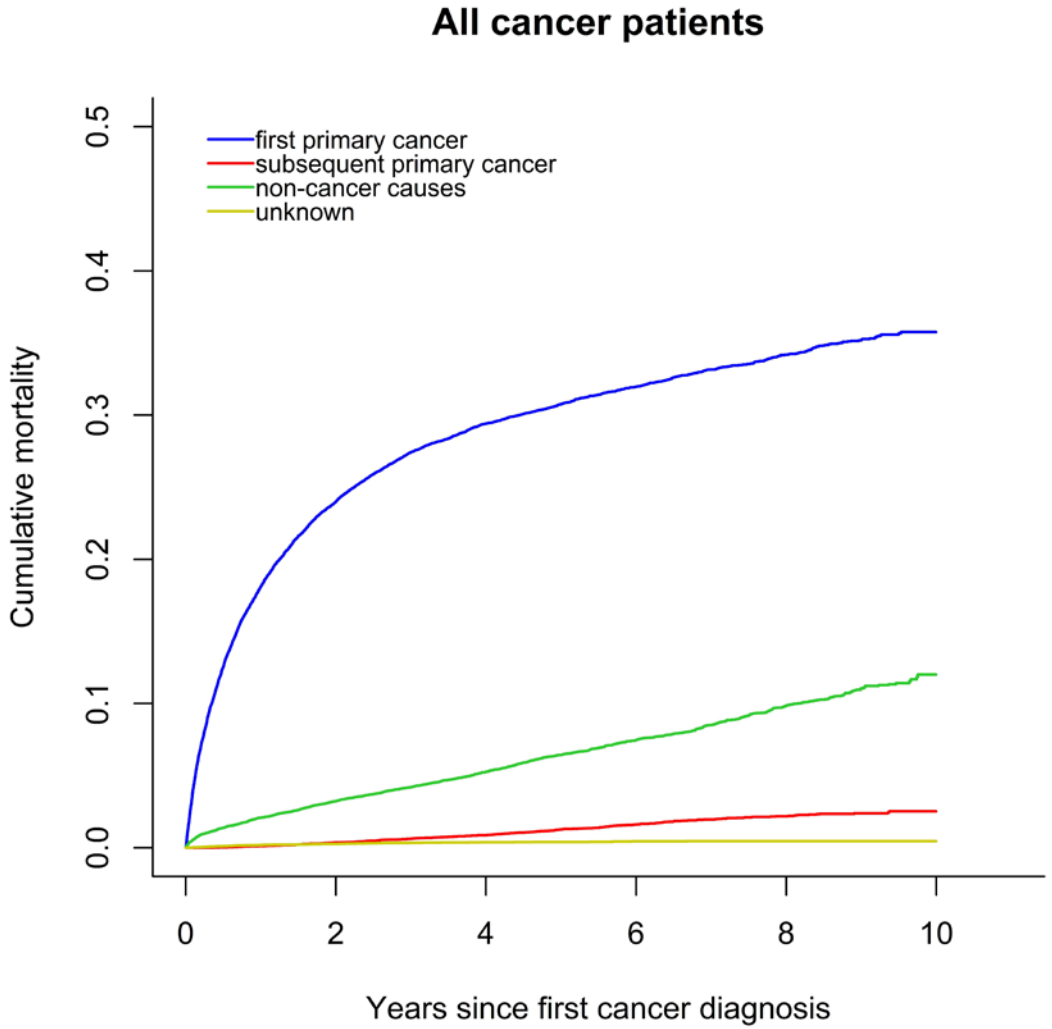
	All non-cancer events			CVD*			Infection			Endocrine			Mental		
	1	5	9	1	5	9	1	5	9	1	5	9	1	5	9
Overall	2.1	6.4	11.0	1.1	3.0	4.9	0.1	0.1	0.3	0.2	0.5	0.7	0.1	0.5	1.0
Sex															
Male	2.3	6.9	11.9	1.2	3.2	5.3	0.1	0.2	0.3	0.2	0.5	0.7	0.1	0.5	1.0
Female	1.8	5.9	9.9	0.9	2.7	4.5	0.1	0.1	0.2	0.1	0.5	0.6	0.1	0.5	1.1
Age at diagnosis															
15-64	0.6	1.7	2.9	0.2	0.7	1.1	0.1	0.1	0.1	0.0	0.1	0.2	<0.1	0.1	0.1
65-74	1.5	4.8	9.6	0.7	2.1	4.2	<0.1	0.1	0.1	0.2	0.6	0.7	<0.1	0.2	0.6
75-84	3.9	12.5	22.6	2.1	6.0	9.9	0.1	0.3	0.6	0.4	0.9	1.4	0.1	1.0	2.5
85+	9.0	26.7	35.3	5.0	13.1	18.1	0.1	0.4	0.7	0.3	1.0	1.3	0.5	2.9	4.4
First cancer sites															
Head and neck	1.5	6.4	14.8	0.3	2.5	6.6	<0.1	0.1	0.1	<0.1	0.1	0.4	0.2	0.6	1.3
Digestive, except colorectal	2.2	3.9	5.3	0.9	1.7	2.3	0.1	0.2	0.2	0.1	0.1	0.3	0.1	0.3	0.3
Colorectal	2.7	8.1	15.1	1.6	4.3	7.4	0.1	0.3	0.3	0.3	0.8	1.1	<0.1	0.4	1.7
Lung	3.2	5.8	6.9	1.3	2.3	2.9	0.1	0.1	0.1	0.2	0.3	0.3	<0.1	<0.1	<0.1
Haematological	4.0	10.9	16.2	1.9	4.6	7.6	0.1	0.2	0.2	0.1	0.8	1.1	0.3	0.7	0.7
skin	1.7	7.1	12.0	0.9	3.2	4.8	<0.1	0.2	0.2	0.1	0.5	0.7	0.1	1.0	1.9
Breast	0.7	4.5	8.1	0.4	1.9	3.4	<0.1	<0.1	0.1	<0.1	0.4	0.4	<0.1	0.7	1.0
Female organs	0.9	3.6	6.4	0.6	1.5	1.9	<0.1	<0.1	0.7	0.1	0.4	0.6	<0.1	0.2	0.5
Prostate	1.5	6.4	13.5	0.9	3.1	6.1	<0.1	0.1	0.2	0.2	0.4	0.6	0.1	0.6	1.2
Urinary tract	2.9	11.3	16.4	1.7	5.9	8.1	0.2	0.3	0.8	0.2	0.7	1.1	0.1	0.7	0.8
Other	2.2	3.7	4.7	0.9	1.3	1.7	0.1	0.1	0.1	0.3	0.4	0.6	<0.1	0.2	0.5
Lymphoma	2.8	6.4	11.0	1.3	3.3	4.9	0.1	0.1	0.1	0.3	0.7	0.7	<0.1	<0.1	1.3

Continued

	Nervous			Respiratory			Digestive			Genitourinary			Others		
	1	5	9	1	5	9	1	5	9	1	5	9	1	5	9
Overall	0.1	0.2	0.5	0.3	1.1	1.9	0.1	0.3	0.5	0.1	0.2	0.3	0.2	0.5	1.0
Sex															
Male	0.1	0.2	0.4	0.3	1.2	2.1	0.1	0.3	0.5	0.1	0.2	0.4	0.2	0.6	1.1
Female	<0.1	0.2	0.5	0.4	1.0	1.6	0.1	0.3	0.5	0.1	0.2	0.2	0.1	0.4	0.7
Age at diagnosis															
15-64	<0.1	0.1	0.2	0.1	0.2	0.5	0.1	0.2	0.3	<0.1	<0.1	<0.1	0.1	0.3	0.4
65-74	0.1	0.2	0.3	0.2	1.0	2.2	0.1	0.2	0.4	<0.1	0.2	0.2	0.1	0.4	0.8
75-84	<0.1	0.4	1.1	0.7	2.3	3.7	0.1	0.5	0.8	0.1	0.3	0.9	0.3	0.7	1.8
85+	0.1	1.0	1.1	1.3	3.8	4.8	0.4	1.2	1.4	0.5	1.4	1.5	0.7	1.8	2.1
First cancer sites															
Head and neck	<0.1	0.2	0.4	0.3	1.4	2.3	0.3	0.9	1.1	<0.1	<0.1	<0.1	0.2	0.6	2.4
Digestive, except colorectal	0.1	0.1	0.1	0.4	0.5	0.7	0.3	0.5	0.5	0.1	0.2	0.6	0.1	0.2	0.2
Colorectal	<0.1	0.2	0.7	0.3	1.1	2.0	0.2	0.5	0.8	<0.1	0.1	0.3	0.2	0.6	0.8
Lung	<0.1	0.2	0.2	1.0	2.0	2.4	<0.1	0.2	0.2	<0.1	0.2	0.2	0.3	0.6	0.6
Haematological	<0.1	0.2	0.4	0.9	2.3	3.7	<0.1	0.1	0.3	0.2	0.7	0.9	0.5	1.2	1.4
skin	0.2	0.4	0.7	0.1	0.9	1.8	<0.1	0.2	0.2	<0.1	0.2	0.5	0.2	0.5	1.1
Breast	0.2	0.3	0.7	0.2	0.6	1.4	<0.1	0.2	0.3	<0.1	0.1	0.1	0.1	0.2	0.7
Female organs	<0.1	0.1	0.1	<0.1	0.4	0.7	0.1	0.7	1.6	0.1	0.1	0.1	<0.1	0.3	0.3
Prostate	0.1	0.3	0.5	0.1	1.0	2.3	0.0	0.2	0.6	0.1	0.3	0.4	0.1	0.6	1.5
Urinary tract	<0.1	0.3	0.8	0.3	1.7	2.1	0.2	0.6	0.6	0.1	0.5	0.7	0.2	0.7	1.5
Other	0.2	0.2	0.2	0.3	0.7	0.7	0.1	0.1	0.1	0.1	0.2	0.2	0.2	0.4	0.7
Lymphoma	<0.1	0.1	0.1	0.6	1.3	2.9	0.1	0.3	0.3	0.1	0.1	0.1	0.1	0.5	0.5

*CVD: Cardiovascular disease.

Figure 6.3: Cumulative incidence function curves for cause-specific deaths.



6.4.2 SMRs and AERs for non-cancer events

For cause of death due to CVD, the overall mortality risk was no greater than expected in the general population (SMR, 0.97; 95%CI 0.90-1.04) (Table 6.4). The SMRs for CVD was significantly lower than expected for individuals with a first cancer diagnosis at age 75-84 years (SMR, 0.82; 95%CI 0.74-0.92). For the oldest cancer patients (age 85+ years at first cancer diagnosis), although the CVD mortality was not significantly higher than in the general population (SMR, 1.09; 95%CI 0.95-1.25), the AER was greatest in this age group (AER, 57.1/10,000 PYR). The SMR and AER for CVD declined with increasing duration of follow-up but were significantly increased within one year of a cancer diagnosis (SMR, 1.44; 95%CI 1.26-1.64; AER, 36.8/10,000 PYR). The SMR and AER for CVD varied by first cancer site showing an increased risk after a first diagnosis of lung cancer (SMR, 1.84; 95%CI 1.39-2.44; AER, 77.4/10,000 PYR), haematological malignancies (SMR, 1.53; 95%CI 1.17-2.00; AER, 49.4/10,000 PYR) and urinary tract cancers (SMR, 1.31; 95%CI 1.04-1.65; AER, 34.1/10,000 PYR).

For cause of death due to other non-cancer events, the SMRs were significantly increased for infectious disease (SMR, 1.56; 95%CI 1.11-2.14) and respiratory disease (SMR, 1.17; 95%CI 1.04-1.32). The SMRs for infectious disease, respiratory disease and digestive disease were significantly elevated for younger cancer patients (those with a first cancer diagnosis at 15-64 years). Within one year from cancer diagnosis, cancer patients had a significantly higher risk of death due to infectious disease, endocrine disease, respiratory disease and digestive disease. For patients with specific cancer types, the SMR for respiratory disease was greatest among individuals with a first diagnosis of lung cancer (SMR, 5.00; 95%CI 3.67-6.82), generating an AER of 112.8/10000 PYR. For other increased SMRs by first cancer types, the

observed number of deaths were generally small (less than 10) and the increase may have occurred by chance alone.

Table 6.4: Standardized mortality ratios (SMRs) and absolute excess risks (AERs) for specific non-cancer disease by sex, age at first cancer diagnosis, follow-up intervals and first cancer sites

	CVD*			Infection			Endocrine			Mental		
	Obs	SMR (95% CI)	AER	Obs	SMR (95% CI)	AER	Obs	SMR (95% CI)	AER	Obs	SMR (95% CI)	AER
Overall	741	0.97 (0.90 to 1.04)	-2.7 (-8.7 to 3.3)	39	**1.56** (1.11 to 2.14)	**1.6** (0.2 to 3.0)	111	0.90 (0.74 to 1.08)	-1.4 (-3.7 to 0.9)	124	**0.75** (0.63 to 0.90)	**-4.6** (-7.0 to -2.1)
Sex												
Male	447	0.93 (0.85 to 1.02)	-6.6 (-14.8 to 1.6)	27	**1.79** (1.22 to 2.60)	**2.3** (0.3 to 4.4)	65	0.84 (0.66 to 1.07)	-2.4 (-5.6 to 0.7)	67	**0.74** (0.58 to 0.94)	**-4.7** (-7.9 to -1.5)
Female	294	1.03 (0.92 to 1.16)	2.5 (-6.3 to 11.3)	12	1.22 (0.69 to 2.15)	0.6 (-1.2 to 2.4)	46	1.00 (0.75 to 1.33)	0.0 (-3.5 to 3.5)	57	0.77 (0.60 to 1.00)	**-4.4** (-8.2 to -0.5)
Age at diagnosis												
15-64	74	1.23 (0.98 to 1.54)	2.9 (-0.7 to 6.5)	10	**2.87** (1.55 to 5.34)	**1.4** (0.1 to 2.7)	12	0.90 (0.51 to 1.59)	-0.3 (-1.7 to 1.2)	5	1.09 (0.45 to 2.61)	0.1 (-0.8 to 1.0)
65-74	160	1.07 (0.92 to 1.25)	4.2 (-5.7 to 14.0)	6	1.06 (0.48 to 2.37)	0.1 (-1.8 to 2.1)	34	1.07 (0.76 to 1.50)	0.9 (-3.7 to 5.4)	14	0.62 (0.37 to 1.04)	**-3.4** (-6.3 to -0.5)
75-84	302	**0.82** (0.74 to 0.92)	**-47.2** (-72.0 to -22.3)	16	1.46 (0.89 to 2.38)	3.7 (-2.0 to 9.4)	49	0.88 (0.66 to 1.16)	-5.0 (-15.0 to 5.0)	58	**0.65** (0.51 to 0.85)	**-22.4** (-33.3 to -11.5)
85+	205	1.09 (0.95 to 1.25)	57.1 (-37.4 to 151.6)	7	1.44 (0.69 to 3.02)	7.2 (-10.3 to 24.7)	16	0.72 (0.44 to 1.17)	-21.4 (-47.8 to 5.0)	47	0.97 (0.73 to 1.29)	-4.7 (-49.9 to 40.6)
Follow-up group												
< 1 y	228	**1.44** (1.26 to 1.64)	**36.8** (21.1 to 52.5)	15	**3.38** (2.04 to 5.60)	**5.6** (1.6 to 9.6)	36	**1.43** (1.03 to 1.98)	5.8 (-0.5 to 12.0)	15	**0.51** (0.31 to 0.84)	**-7.8** (-11.8 to -3.7)
1-4 y	354	**0.83** (0.75 to 0.92)	**-14.0** (-21.2 to -6.8)	15	1.08 (0.65 to 1.78)	0.2 (-1.3 to 1.7)	55	0.79 (0.60 to 1.02)	**-2.9** (-5.8 to -0.1)	74	0.80 (0.64 to 1.01)	**-3.5** (-6.8 to -0.2)
5-9 y	159	0.88 (0.76 to 1.03)	-11.4 (-24.7 to 1.9)	9	1.37 (0.71 to 2.64)	1.3 (-1.8 to 4.5)	20	0.71 (0.46 to 1.10)	-4.4 (-9.1 to 0.3)	35	0.82 (0.59 to 1.14)	-4.2 (-10.4 to 2.1)
First cancer sites												
Head and neck	30	0.94 (0.66 to 1.35)	-4.7 (-31.6 to 22.2)	1	0.95 (0.13 to 6.74)	-0.1 (-5.0 to 4.8)	2	0.40 (0.10 to 1.58)	**-7.6** (-14.6 to -0.7)	8	1.18 (0.59 to 2.36)	3.0 (-10.9 to 16.9)
Digestive, except colorectal	28	1.07 (0.74 to 1.55)	7.2 (-34.6 to 49.0)	4	**4.88** (1.83 to 13.01)	12.8 (-3.0 to 28.6)	3	0.72 (0.23 to 2.24)	-4.7 (-18.3 to 9.0)	4	0.71 (0.27 to 1.89)	-6.6 (-22.4 to 9.2)
Colorectal	151	1.03 (0.88 to 1.21)	3.2 (-15.6 to 22.0)	8	1.69 (0.84 to 3.38)	2.5 (-1.8 to 6.9)	26	1.12 (0.76 to 1.65)	2.2 (-5.6 to 10.0)	20	**0.59** (0.38 to 0.91)	**-11.0** (-17.9 to -4.2)
Lung	48	**1.84** (1.39 to 2.44)	**77.4** (29.5 to 125.2)	3	**3.69** (1.19 to 11.44)	7.7 (-4.3 to 19.7)	6	1.39 (0.62 to 3.09)	5.9 (-11.0 to 22.8)	0	-	-18.9
Hematological	53	**1.53** (1.17 to 2.00)	**49.1** (10.8 to 87.4)	2	1.78 (0.45 to 7.13)	2.4 (-5.1 to 9.8)	8	1.44 (0.72 to 2.88)	6.6 (-8.3 to 21.5)	6	0.79 (0.36 to 1.76)	-4.2 (-17.1 to 8.7)
Skin	78	0.82 (0.66 to 1.02)	-15.4 (-30.9 to 0.1)	4	1.31 (0.49 to 3.48)	0.8 (-2.7 to 4.3)	12	0.82 (0.47 to 1.45)	-2.3 (-8.4 to 3.7)	26	1.21 (0.82 to 1.78)	4.0 (-4.9 to 13.0)
Breast	61	0.89 (0.69 to 1.14)	-5.7 (-16.8 to 5.5)	2	0.79 (0.20 to 3.18)	-0.4 (-2.4 to 1.6)	9	0.77 (0.40 to 1.47)	-2.0 (-6.3 to 2.3)	16	0.94 (0.57 to 1.53)	-0.8 (-6.5 to 4.9)

Female organs	13	0.71 (0.41 to 1.23)	-15.0 (-35.1 to 5.2)	2	3.04 (0.76 to 12.14)	3.8 (-4.1 to 11.7)	5	1.53 (0.64 to 3.68)	4.9 (-7.5 to 17.4)	2	0.45 (0.11 to 1.80)	-6.9 (-14.8 to 1.0)
Prostate	161	**0.73** (0.62 to 0.85)	**-27.4** (-38.7 to -16.0)	6	0.85 (0.38 to 1.90)	-0.5 (-2.7 to 1.7)	20	**0.55** (0.36 to 0.86)	**-7.3** (-11.3 to -3.4)	28	**0.68** (0.47 to 0.98)	**-6.1** (-10.8 to -1.4)
Urinary tract	71	**1.31** (1.04 to 1.65)	**34.1** (0.7 to 67.5)	5	**2.97** (1.24 to 7.14)	6.7 (-2.2 to 15.6)	9	1.06 (0.55 to 2.04)	1.1 (-10.8 to 13.0)	8	0.69 (0.35 to 1.39)	-7.2 (-18.4 to 4.0)
Lymphoma	26	1.27 (0.86 to 1.86)	18.0 (-14.7 to 50.8)	1	1.42 (0.19 to 9.75)	1.0 (-5.4 to 7.4)	4	1.17 (0.44 to 3.13)	1.9 (-10.9 to 14.8)	2	0.45 (0.11 to 1.80)	-8.0 (-17.0 to 1.1)
Others	21	1.00 (0.65 to 1.54)	0.1 (-20.0 to 20.1)	1	1.37 (0.20 to 10.10)	0.6 (-3.8 to 5.0)	7	2.02 (0.96 to 4.24)	7.9 (-3.7 to 19.4)	4	0.88 (0.33 to 2.34)	-1.2 (-10.0 to 7.5)

Continued

	Nervous			Respiratory			Digestive			Genitourinary		
	Obs	SMR (95% CI)	AER	Obs	SMR (95% CI)	AER	Obs	SMR (95% CI)	AER	Obs	SMR (95% CI)	AER
Overall	62	**0.59** (0.45 to 0.76)	**-4.8** (-6.5 to -3.1)	271	**1.17** (1.04 to 1.32)	**4.5** (0.8 to 8.1)	79	0.99 (0.78 to 1.23)	-0.1 (-2.1 to 1.9)	52	0.98 (0.73 to 1.29)	-0.1 (-1.7 to 1.5)
Sex												
Male	35	**0.54** (0.39 to 0.76)	**-5.8** (-8.1 to -3.5)	168	1.09 (0.94 to 1.27)	2.8 (-2.2 to 7.8)	44	0.93 (0.69 to 1.24)	-0.7 (-3.3 to 1.9)	34	1.09 (0.78 to 1.52)	0.5 (-1.7 to 2.8)
Female	27	**0.67** (0.46 to 0.98)	**-3.4** (-6.1 to -0.8)	103	**1.33** (1.10 to 1.61)	**6.7** (1.5 to 11.9)	35	1.08 (0.78 to 1.51)	0.7 (-2.3 to 3.7)	18	0.83 (0.52 to 1.32)	-1.0 (-3.1 to 1.2)
Age at diagnosis												
15-64	9	0.78 (0.41 to 1.50)	-0.5 (-1.8 to 0.7)	30	**1.45** (1.01 to 2.07)	2.0 (-0.3 to 4.3)	21	**1.78** (1.16 to 2.73)	**2.0** (0.1 to 3.9)	2	0.91 (0.23 to 3.65)	0.0 (-0.6 to 0.6)
65-74	14	**0.57** (0.34 to 0.96)	**-4.2** (-7.1 to -1.3)	76	1.24 (0.99 to 1.55)	5.8 (-1.0 to 12.6)	13	0.71 (0.41 to 1.22)	-2.1 (-4.9 to 0.7)	9	1.03 (0.54 to 1.98)	0.1 (-2.2 to 2.4)
75-84	25	**0.51** (0.35 to 0.76)	**-17.3** (-24.4 to -10.1)	111	1.04 (0.86 to 1.25)	3.0 (-12.1 to 18.0)	27	0.79 (0.54 to 1.16)	-5.1 (-12.6 to 2.3)	21	0.76 (0.50 to 1.17)	-4.8 (-11.4 to 1.7)
85+	14	0.71 (0.42 to 1.20)	-19.3 (-44.0 to 5.4)	54	1.28 (0.98 to 41.67)	39.7 (-8.8 to 88.2)	18	1.15 (0.72 to 1.82)	7.8 (-20.2 to 35.8)	20	1.39 (0.90 to 2.15)	18.8 (-10.7 to 48.4)
Follow-up group												
< 1 y	11	0.57 (0.31 to 1.02)	**-4.5** (-7.9 to -1.0)	69	**1.54** (1.22 to 1.95)	**12.9** (4.2 to 21.5)	24	**1.51** (1.01 to 2.25)	4.3 (-0.8 to 9.4)	14	1.33 (0.79 to 2.25)	1.8 (-2.0 to 5.7)
1-4 y	34	**0.59** (0.42 to 0.83)	**-4.6** (-6.8 to -2.4)	144	1.11 (0.95 to 1.31)	2.9 (-1.7 to 7.5)	38	0.85 (0.62 to 1.17)	-1.3 (-3.7 to 1.0)	29	0.99 (0.69 to 1.43)	0.0 (-2.1 to 2.0)
5-9 y	17	**0.62** (0.38 to 0.99)	**-5.7** (-10.0 to -1.3)	58	1.01 (0.78 to 1.31)	0.4 (-7.6 to 8.4)	17	0.88 (0.55 to 1.42)	-1.2 (-5.6 to 3.1)	9	0.68 (0.36 to 1.31)	-2.2 (-5.4 to 0.9)
First cancer sites												
Head and neck	3	0.69 (0.22 to 2.15)	-3.3 (-11.8 to 5.2)	14	1.47 (0.87 to 2.48)	11.2 (-7.1 to 29.6)	8	**2.39** (1.20 to 4.78)	11.7 (-2.2 to 25.5)	0	-	-5.4
Digestive, except colorectal	1	0.29 (0.04 to 2.05)	**-9.9** (-17.8 to -2.0)	9	1.19 (0.62 to 2.29)	5.8 (-17.9 to 29.5)	8	**3.00** (1.50 to 5.99)	21.5 (-0.9 to 43.8)	5	**2.72** (1.13 to 6.53)	12.7 (-4.9 to 30.4)
Colorectal	8	**0.41** (0.20 to 0.81)	**-9.2** (-13.5 to -4.8)	40	0.95 (0.69 to 1.29)	-1.8 (-11.5 to 7.9)	16	1.06 (0.65 to 1.74)	0.7 (-5.4 to 6.9)	4	0.38 (0.14 to 1.01)	**-5.1** (-8.2 to -2.0)
Lung	2	0.57 (0.14 to 2.29)	-5.3 (-15.1 to 4.5)	40	**5.00** (3.67 to 6.82)	**112.8** (69.1 to 156.5)	3	1.11 (0.36 to 3.43)	1.0 (-11.0 to 13.0)	3	1.63 (0.53 to 5.06)	4.1 (-7.9 to 16.1)
Hematological	3	0.64 (0.21 to 1.99)	-4.5 (-13.6 to 4.6)	25	**2.44** (1.65 to 3.61)	**39.6** (13.3 to 65.9)	2	0.55 (0.14-2.20)	-4.4 (-11.8 to 3.0)	8	**3.32** (1.66 to 6.63)	**15.0** (0.1 to 29.9)
Skin	10	0.79 (0.42 to 1.46)	-2.4 (-8.0 to 3.1)	23	0.84 (0.56 to 1.27)	-3.9 (-12.3 to 4.5)	4	0.41 (0.15 to 1.10)	**-5.1** (-8.6 to -1.6)	5	0.74 (0.31 to 1.78)	-1.6 (-5.5 to 2.4)
Breast	11	1.05 (0.58 to 1.90)	0.4 (-4.3 to 5.1)	20	0.97 (0.63 to 1.51)	-0.4 (-6.8 to 6.0)	6	0.72 (0.32 to 1.60)	-1.7 (-5.2 to 1.8)	3	0.57 (0.19 to 1.78)	-1.6 (-4.1 to 0.9)
Female organs	1	0.35 (0.05 to 2.50)	-5.2 (-10.8 to 0.4)	4	0.70 (0.26 to 1.88)	-4.8 (-16.0 to 6.4)	8	**3.57** (1.78 to 7.14)	**16.4** (0.6 to 32.2)	1	0.72 (0.10 to 5.11)	-1.1 (-6.7 to 4.5)

Prostate	13	**0.43** (0.25 to 0.75)	**-7.7** (-10.9 to -4.5)	54	**0.75** (0.58 to 0.98)	**-8.1** (-14.6 to -1.5)	14	0.63 (0.38 to 1.07)	**-3.7** (-7.0 to -0.3)	13	0.91 (0.53 to 1.58)	-0.6 (-3.8 to 2.7)
Urinary tract	6	0.84 (0.38 to 1.87)	-2.3 (-12.0 to 7.4)	21	1.31 (0.85 to 2.01)	10.0 (-8.1 to 28.2)	6	1.10 (0.50 to 2.46)	1.2 (-8.6 to 10.9)	6	1.61 (0.72 to 3.57)	4.6 (-5.1 to 14.3)
Lymphoma	1	0.35 (0.05 to 2.46)	-6.2 (-12.6 to 0.2)	11	1.77 (0.98 to 3.19)	15.6 (-5.7 to 36.9)	2	0.89 (0.22 to 3.56)	-0.8 (-9.9 to 8.3)	1	0.71 (0.10 to 5.05)	-1.3 (-7.7 to 5.1)
Others	3	1.02 (0.33 to 3.15)	0.1 (-7.5 to 7.7)	10	1.66 (0.89 to 3.08)	8.9 (-5.0 to 22.7)	2	0.83 (0.21 to 3.34)	-0.9 (-7.1 to 5.3)	3	2.08 (0.67 to 6.46)	3.5 (-4.1 to 11.0)

*CVD: Cardiovascular disease. Bold numbers indicated statistically significance.

6.5 Discussion

This population-based study identified that CVD was the leading cause of competing mortality among Tasmanian cancer patients diagnosed from 2006 to 2013. CVD mortality exceeded mortality due to SPCs and other non-cancer events for individuals with a first cancer diagnosis at age 65 years or older and was greatest for those aged 85 or above. For the whole follow-up period, CVD mortality risk among cancer patients were as expected for the general population but significantly higher than expected in the first year of diagnosis. For other non-cancer events, cancer patients were significantly more likely to die from infectious disease and respiratory disease than the general population, particularly those with a younger age at diagnosis and in the first year of follow-up.

The high CVD mortality among patients with a cancer diagnosis at age 65 years or older is consistent with general population mortality rates. However, for individuals with a cancer diagnosis at the oldest ages (85 years or older), a greater excess CVD mortality burden was observed than in other age groups. A slight increase in the SMR can produce a large increase in the AER when the expected mortality burden in the general population is high (e.g. high CVD mortality in an older population) [23]. In our cohort, the proportion of deaths due to heart failure increased from 1.4% of all CVD deaths for age 15-64 years to 11.7% of all CVD deaths for those aged 85 years or older at cancer diagnosis (Table 6.5). Other common causes of CVD deaths for age 85+ years include deaths due to chronic ischemic heart disease (22.9%), stroke (17.1%) and acute myocardial infarction (14.6%). The great excess burdens of CVD deaths were observed among colorectal, hematologic and urinary tract cancer patients but not for other cancer types. In the absence of treatment data in this population-based cancer registry, it is unclear whether cardiotoxicity caused by anticancer treatment played a role, but the literature has demonstrated connections between conventional

anticancer drugs (e.g. anthracyclines, cyclophosphamide and fluoropyrimidines), novel targeted cancer therapies (e.g. kinase inhibitors) and cardiac dysfunction including heart failure, vascular thrombosis and cardiac ischemia [11, 24, 25]. Opportunities for better cardioprotective interventions might be considered for the oldest cancer patients and for patients with a first diagnosis of colorectal, hematologic and urinary tract cancer.

Our finding of a significantly increased risk of CVD death within one year of a cancer diagnosis is consistent with previous studies from Sweden [14] and the United States for any cancer diagnosed from 1973-2012 or for prostate cancer diagnosed from 1979-2004 [10, 15]. Psychological stress is associated with adverse cardiovascular pathophysiological changes [26]. A cancer diagnosis might be an important stressor that triggers CVD death in the short term [14, 15].

For the whole follow-up period, the CVD mortality risk among cancer patients was as expected for the general population. This is in contrast to a previous Australian study that observed the risk of CVD deaths to be higher than expected in the state of Queensland following cancers diagnosed between 1982 and 2002 [9]. Recent advances in cardiovascular imaging, improved treatment and cardioprotective therapy for cancer patients might explain why we did not see an excess CVD mortality risk for cancer diagnosed during 2006-2013, other than in the first year after cancer diagnosis.

For other non-cancer events, the increased SMR for infectious disease is likely attributable to sepsis after cancer diagnosis. In our study, the number of deaths due to sepsis accounted for more than half of all deaths due to infection, and all deaths due to infection in lung cancer patients. These deaths mostly occurred within one year after cancer diagnosis. Although clinical guidelines provide recommendations on sepsis prevention and management in

patients with cancer, more efforts should be made to reduce this preventable cause of death during the first year of follow-up [27, 28], especially for lung cancer patients. The increased SMR for respiratory disease is likely because of a high incidence of chronic obstructive pulmonary disease (COPD) among cancer patients, especially for lung cancer patients (67.5% of respiratory deaths were due to COPD, Table 6.6). The pronounced excess mortality due to respiratory disease, particularly COPD, among lung cancer patients may reflect the strong association between lung cancer and other smoking-related diseases [29]. The effects of smoking may also be reflected in the high excess CVD mortality among lung cancer patients. Smoking cessation is therefore essential as the core prevention activity to reduce tobacco-related deaths. However, the capacity to reduce CVD deaths in lung cancer patients may be limited given their short median survival time.

Our finding of a lower risk of CVD deaths among prostate cancer patients than in the general population is consistent with a previous finding from the Swedish national prostate cancer registry [30]. This apparent decreased risk may be partially explained by self-selection of relatively health-conscious men undergoing Prostate Specific Antigen (PSA) testing with a subsequent diagnosis of prostate cancer.

It is interesting to note that there was no increase in deaths from mental disorders or nervous system diseases among cancer patients when compared to the general population. This finding is consistent with previous findings using data from the World Mental Health Surveys between 2001-2011 [31] which showed similar rates of common mental disorders among cancer survivors and cancer-free respondents.

A major strength of our study was the focus on non-cancer mortality in a recent population-based cohort with a combination of internal comparisons considering the presence of

competing risks, and external comparisons with the general population. To the best of our knowledge, only one other study has reported non-cancer mortality due to a variety of causes among cancer patients in recent times. The authors concluded that the risk of non-cancer deaths now exceeds the risk of cancer deaths, but did not account for follow-up time nor the presence of competing risks [10]. In our study in Tasmania, first cancers were still the leading cause of death among individuals with cancer diagnosis between 2006-2013. Careful interpretation is needed when comparing cancer mortality risk with non-cancer mortality risk, especially in cohorts with high competing risks [20]. Limitations of our study include the relatively short follow-up time, the lack of data on cancer treatment and history of other diseases prior to and/or after cancer diagnosis, which prohibited examination of long-term cause-specific mortality and the possible adverse effects of cancer treatments.

In conclusion, CVD was the most likely competing cause of death among Tasmanian cancer patients in recent years, particularly for individuals diagnosed with cancer at age 65 or above. Although CVD mortality among cancer patients was no greater than expected from the general population overall, interventions to reduce the risk of CVD deaths within the first year after cancer diagnosis should be considered. The increased risk of death due to infectious disease and respiratory disease suggests opportunities for better prevention.

Table 6.5: Number of CVD deaths among cancer patients with all first cancer sites combined, by age at first cancer diagnosis

Age at first cancer diagnosis 15-64y					Age at first cancer diagnosis 65-74y			
Cause of death	ICD10 code	No.	Percent		Cause of death	ICD10 code	No.	Percent
Total		74	100.0%		Total		160	100.0%
Hypertensive heart disease	I11	1	1.4%		Essential (primary) hypertension	I10	2	1.3%
Acute myocardial infarction	I21	15	20.3%		Hypertensive renal disease	I12	1	0.6%
Other acute ischemic heart diseases	I24	2	2.7%		Hypertensive heart and renal disease	I13	2	1.3%
Chronic ischemic heart disease	I25	21	28.4%		Acute myocardial infarction	I21	28	17.5%
Other diseases of pericardium	I31	2	2.7%		Chronic ischemic heart disease	I25	40	25.0%
Nonrheumatic aortic valve disorders	I35	1	1.4%		Pulmonary embolism	I26	2	1.3%
Cardiomyopathy	I42	6	8.1%		Other pulmonary heart diseases	I27	1	0.6%
Atrial fibrillation and flutter	I48	2	2.7%		Nonrheumatic aortic valve disorders	I35	3	1.9%
Other cardiac arrhythmias	I49	1	1.4%		Endocarditis, valve unspecified	I38	2	1.3%
Heart failure	I50	1	1.4%		Cardiomyopathy	I42	6	3.8%
Subarachnoid hemorrhage	I60	4	5.4%		Cardiac arrest	I46	1	0.6%
Intracerebral hemorrhage	I61	2	2.7%		Atrial fibrillation and flutter	I48	1	0.6%
Other nontraumatic intracranial hemorrhage	I62	2	2.7%		Other cardiac arrhythmias	I49	2	1.3%
Cerebral infarction	I63	2	2.7%		Heart failure	I50	12	7.5%
Stroke, not specified as hemorrhage or infarction	I64	4	5.4%		Complications and ill-defined descriptions of heart disease	I51	7	4.4%
Aortic aneurysm and dissection	I71	2	2.7%		Subarachnoid hemorrhage	I60	1	0.6%
Other peripheral vascular diseases	I73	2	2.7%		Intracerebral hemorrhage	I61	4	2.5%
Phlebitis and thrombophlebitis	I80	2	2.7%		Other nontraumatic intracranial hemorrhage	I62	3	1.9%
Varicose veins of lower extremities	I83	1	1.4%		Cerebral infarction	I63	6	3.8%
Other disorders of veins	I87	1	1.4%		Stroke, not specified as hemorrhage or infarction	I64	21	13.1%
					Other cerebrovascular diseases	I67	1	0.6%
					Sequelae of cerebrovascular disease	I69	4	2.5%
					Aortic aneurysm and dissection	I71	7	4.4%
					Other peripheral vascular diseases	I73	3	1.9%

Continued

Age at first cancer diagnosis 75-84y					Age at first cancer diagnosis 85+ y			
Cause of death	ICD10 code	No.	Percent		Cause of death	ICD10 code	No.	Percent
Total		302	100.0%		Total		205	100.0%
Rheumatic mitral valve diseases	I05	3	1.0%		Rheumatic tricuspid valve diseases	I07	1	0.5%
Essential (primary) hypertension	I10	4	1.3%		Essential (primary) hypertension	I10	7	3.4%
Hypertensive heart disease	I11	6	2.0%		Hypertensive heart disease	I11	5	2.4%
Hypertensive renal disease	I12	3	1.0%		Hypertensive renal disease	I12	1	0.5%
Hypertensive heart and renal disease	I13	2	0.7%		Hypertensive heart and renal disease	I13	1	0.5%
Angina pectoris	I20	2	0.7%		Angina pectoris	I20	1	0.5%
Acute myocardial infarction	I21	48	15.9%		Acute myocardial infarction	I21	30	14.6%
Other acute ischemic heart diseases	I24	7	2.3%		Other acute ischemic heart diseases	I24	2	1.0%
Chronic ischemic heart disease	I25	88	29.1%		Chronic ischemic heart disease	I25	47	22.9%
Pulmonary embolism	I26	3	1.0%		Pulmonary embolism	I26	3	1.5%
Other pulmonary heart diseases	I27	3	1.0%		Other pulmonary heart diseases	I27	6	2.9%
Acute and subacute endocarditis	I33	2	0.7%		Acute and subacute endocarditis	I33	1	0.5%
Nonrheumatic mitral valve disorders	I34	1	0.3%		Nonrheumatic aortic valve disorders	I35	7	3.4%
Nonrheumatic aortic valve disorders	I35	5	1.7%		Endocarditis, valve unspecified	I38	1	0.5%
Endocarditis, valve unspecified	I38	2	0.7%		Cardiomyopathy	I42	2	1.0%
Cardiomyopathy	I42	8	2.6%		Other conduction disorders	I45	1	0.5%
Atrial fibrillation and flutter	I48	11	3.6%		Cardiac arrest	I46	1	0.5%
Other cardiac arrhythmias	I49	3	1.0%		Atrial fibrillation and flutter	I48	2	1.0%
Heart failure	I50	19	6.3%		Heart failure	I50	24	11.7%
Complications and ill-defined descriptions of heart disease	I51	2	0.7%		Complications and ill-defined descriptions of heart disease	I51	8	3.9%
Subarachnoid hemorrhage	I60	1	0.3%		Intracerebral hemorrhage	I61	2	1.0%
Intracerebral hemorrhage	I61	7	2.3%		Other nontraumatic intracranial hemorrhage	I62	1	0.5%
Other nontraumatic intracranial hemorrhage	I62	3	1.0%		Cerebral infarction	I63	1	0.5%
Cerebral infarction	I63	5	1.7%		Stroke, not specified as hemorrhage or infarction	I64	35	17.1%
Stroke, not specified as hemorrhage or infarction	I64	41	13.6%		Sequelae of cerebrovascular disease	I69	6	2.9%
Other cerebrovascular diseases	I67	1	0.3%		Atherosclerosis	I70	1	0.5%
Sequelae of cerebrovascular disease	I69	5	1.7%		Aortic aneurysm and dissection	I71	4	2.0%
Atherosclerosis	I70	2	0.7%		Other peripheral vascular diseases	I73	1	0.5%
Aortic aneurysm and dissection	I71	10	3.3%		Arterial embolism and thrombosis	I74	1	0.5%
Other peripheral vascular diseases	I73	4	1.3%		Phlebitis and thrombophlebitis	I80	1	0.5%
Other venous embolism and thrombosis	I82	1	0.3%		Varicose veins of lower extremities	I83	1	0.5%

Table 6.6: Number of respiratory deaths among lung cancer patients

Cause of death	ICD10 code	No.	Percent
Total		40	100.0%
Influenza due to identified zoonotic or pandemic influenza virus	J09	1	2.5%
Influenza due to identified seasonal influenza virus	J10	1	2.5%
Pneumonia, organism unspecified	J18	5	12.5%
Emphysema	J43	2	5.0%
Chronic obstructive pulmonary disease	J44	27	67.5%
Respiratory conditions due to other external agents	J70	1	2.5%
Other interstitial pulmonary diseases	J84	2	5.0%
Other respiratory disorders	J98	1	2.5%

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Chapter 7: Discussion

7.1 Background

A growing number of individuals are living with a history of cancer in Australia due to increases in cancer incidence and improved cancer survival [1]. In 2012, there were nearly 1 million cancer survivors, representing 4.3% of the Australian population. With the aging population and improved cancer survival, one of the potentially most life-threatening events among these cancer survivors is facing cancer again - the development of MPCs. A research focus on temporal trends in the risk of developing MPCs can provide valuable information to indicate potential changes in factors that relate to MPC development, help predict future rates of MPC occurrence and help guide MPC management planning.

Cancer patients can also experience non-cancer events such as fatal cardiovascular events after a first cancer diagnosis. MPCs and non-cancer events compete with the first cancer as the cause of death. In this era of personalized cancer therapy, monitoring mortality from MPCs and non-cancer events contributes to knowledge of patient outcomes after a first cancer diagnosis, may help to guide individualized treatments, and optimise follow-up care. Using a systematic review and original data from the TCR, this thesis aimed to add to the current literature on temporal trends in the risk of MPCs and competing mortality among patients with adult-onset cancer, through four studies with the following aims:

1. Study 1: To conduct a systematic review of the scientific literature to determine whether the risk of MPCs has increased over recent decades (Chapter 3).
2. Study 2: To investigate trends in the risk of second primary cancer among adult cancer survivors in Tasmania during 1980-2013 (Chapter 4).

3. Study 3: To assess subsequent primary cancer mortality among Tasmanian adult-onset cancer patients in competing risk models and to investigate their patterns since 1980 (Chapter 5).
4. Study 4: To assess the risk of non-cancer deaths among Tasmanian cancer patients in competing risk models during 2006-2015 (Chapter 6).

The following sections provide a summary of the key findings in this thesis, their public health and clinical implications, the limitations of the current studies and future directions.

7.2 Summary of findings

Epidemiological research indicated changing trends in medical investigations, treatment protocols for cancer and environmental and lifestyle factors associated with cancer during recent decades [1-5]. However, whether the risk of MPCs have changed during this period remained unknown. Chapter 3 presented a systematic review of the scientific literature and identified an increasing trend in the risk of developing MPCs from the 1980s to 2000 in the USA and Australia, for all first cancer sites combined. However, evidence of the trend in overall MPC risk since 2000 was limited as described in the systematic review. Chapter 4 extends and progresses findings from the systematic review using original data from the TCR for the period 1980 to 2013. In Tasmania, nearly 10% of adult-onset cancer survivors were diagnosed with MPCs during the past three decades. The risk of second primary cancers increased significantly with periods of first cancer diagnosis from 1980 to 2009.

Traditional survival analyses overestimate mortality risk due to a specific cause, because of the failure to consider the presence of competing risks. To date, there has been limited assessment of mortality from MPCs and non-cancer events in the presence of competing risks. Chapter 5 described temporal trends in MPC mortality since 1980 among adult-onset

cancer patients in competing risk models. The risk of first cancer mortality gradually decreased from 1980-2009, whereas the risk of MPC mortality increased in later time periods relative to 1980-1984, and was highest for individuals with a first cancer diagnosis in the 1990s. Chapter 6 identified that CVD was the leading cause of competing mortality among Tasmanian cancer patients diagnosed from 2006-2013. The risks of death due to specific non-cancer events were higher than expected during the first year after a cancer diagnosis.

7.3 Implications of Research

The implementation of cancer screening programs and increased use of medical imaging has promoted the early diagnosis of cancer, but also contributed to the detection of cancers that are slow- or even non-progressive, and potential overdiagnosis in cancer [6]. Overdiagnosis due to population-based cancer screening in the general population has been well recognised [6-11]. Our finding of an increasing trend in the risk of developing MPCs from the 1980s to 2000 in the USA and Australia may reflect an increase in the use of medical investigations among cancer survivors over this period. In Tasmania, site-specific time trends in the risk of MPCs were generally consistent with changing patterns of cancer screening interventions, particularly PSA testing and use of medical imaging for specific cancer types. Patient anxiety after a first cancer diagnosis may result in overestimation of the benefits and underestimation of the potential harms of cancer screening in the case of overdiagnosis. In addition, frequent medical imaging during post-treatment surveillance may increase the chance of detecting indolent MPCs. Our long-term surveillance on the risk of MPCs over time provides valuable information for predicting future MPC occurrence rates, and supports the need for future investigation into the mode of MPC diagnosis. Although some international evidence has found that cancer patients were more likely to participate in cancer screening than the general population [12, 13], this is unknown for Australia given the lack of information on mode of MPC

ascertainment. Assessing the mode of MPC diagnosis will help to delineate whether overdiagnosis has occurred in the detection of MPCs. The increased risk of smoking related MPCs in recent periods also supports the potential of MPC prevention strategies. Cessation of cigarette smoking may help to reduce the risk of developing smoking-related MPCs. However, there are no known data quantifying the effect size of smoking cessation after the diagnosis of a first cancer on reducing the risk of smoking-related MPCs. Studies that specifically examine the effect of smoking cessation on MPC prevention are therefore recommended.

The increased risk of MPC mortality for a first cancer diagnosed in the 1990s may reflect a combination of greater detection of non-fatal first cancers during this period and/or adverse late effects of cancer treatment. The detection of prostate cancer increased dramatically in Tasmania in the 1990s, strongly influenced by intensive use of PSA testing. However, PSA-based screening may be associated with a high risk of overdiagnosis [7, 9, 11]. If a large number of 'first cancers' were overdiagnosed, a life-threatening MPC will be registered as a 'subsequent cancer'. Therefore, an increase in the mortality related to MPCs will consequently occur. In the case of greater detection of non-fatal first cancers, another concern arises from the adverse late effects of cancer treatment, which may induce life-threatening MPCs. Monitoring time trends in competing mortality from MPCs could help inform clinicians, policy-makers and patients about the potential harms of increased detection of non-fatal first cancers and the potential risk of treatment-related MPCs.

With the aging population in Australia, the burden of chronic disease, especially CVD will increase among older cancer patients. Our finding of an excess burden of CVD among individuals with a cancer diagnosis at age ≥ 85 years suggests that treating clinicians might consider advising on CVD prevention strategies for this population. The increased mortality

risk due to specific non-cancer disease during the first year of follow-up helped to identify diseases that require prevention, early detection, and/or more effective treatment after a cancer diagnosis. Current evidence-based cancer guidelines generally focused on cancer-associated disease, cancer treatment-induced disease or cancer-related symptoms [14]. Our research on current non-cancer mortality among cancer patients contributes to the evidence base to optimise current follow-up guidelines and thereby inform clinicians of how to improve the management of non-cancer events among cancer patients.

7.4 Limitations in current studies

The major limitations of the studies presented in this thesis are the lack of data on the mode of MPC ascertainment and treatment information of the first primary cancer, which prevented a more precise interpretation of the results. The TCR is a population-based cancer registry that collects demographic data and basic histopathological characteristics such as cancer site and morphology. Detailed histopathological data such as tumour stage, tumour grade were not available for all cancer types, nor are tumour biomarkers and tumour genetics collected, which prohibited complete analyses for risk stratification. Lack of treatment information precluded the evaluation of treatment effect on patient outcomes. These limitations, however, can be at least partially overcome through future projects linking the TCR database with Tasmanian public hospital administrative data.

Other limitations relate to the underascertainment of MPCs due to out-migration of the Tasmanian cancer patients. The Australian Cancer Database (ACD) is managed by the Australian Institute of Health and Welfare (AIHW) and includes data for all cancers diagnosed in Australia since 1982 (excluding basal and squamous cell carcinomas of the skin). Some states and territories provide borderline, uncertain and in-situ neoplasms for

certain topographies as part of annual data submissions, however the routine reporting of data by the AIHW focuses on invasive tumours only. On an annual basis, the AIHW undertakes a process of data-deduplication where it applies probabilistic data linkage techniques to identify potential duplicate records across jurisdictions to limit the risk of duplicate reporting. The TCR does not undertake any routine matching of Tasmanian cases to other Australian state and territory cancer records stored in the ACD, but does update its records where it becomes aware of the existence of duplicate tumour registrations in other states of territories. However, we determined that in our study period the proportion of all Tasmanian cancer cases with MPCs registered in another Australian jurisdiction was very small (0.34%, personal communication, Manager, Australian Cancer Database). The relatively small Tasmanian population limits statistical power for less common cancer types. However, less common cancer types were never specifically investigated in this thesis. The TCR data has a particular advantage due to the relative stable population (less out-migration) of the Tasmanian population. Further, given similar characteristics to populations in other Australian jurisdictions, the findings were considered generalisable.

7.5 Future directions

In this thesis, we have presented a systematic review of the time trends in the risk of developing MPCs worldwide, and several novel findings of the temporal trends in the risk of MPCs, competing mortality due to MPCs, and competing mortality due to non-cancer events among adult-onset cancer patients in the state of Tasmania, Australia. On the basis of this research, it is identified that further research is necessary with regard to mode of MPC diagnosis and management of patient outcomes after first cancer diagnosis, including MPCs and non-cancer events to improve the prognosis of cancer patients. Directions for future research could include the following:

- Identify the mode of MPC diagnosis. Chapters 3 and 4 reported an increasing trend in the risk of MPCs over time. As cancer patients may receive more frequent medical examination than the general population, it is necessary to identify how the subsequent primary cancer is diagnosed, by the patient as a result of symptoms, by cancer screening, or through a routine follow-up examination. The mode of MPC diagnosis helps to indicate if the subsequent primary cancer is delayed diagnosis, i.e. diagnosed at an advanced stage, diagnosed at an early stage, or overdiagnosed respectively.
- Identify and quantify any overdiagnosis of MPCs among cancer survivors, and thus assess whether there is potential for optimizing follow-up guidelines. This concern arises because screening tests and medical imaging for some cancer types in the general population were associated with overdiagnosis, thus it is equally important to determine whether the mode of MPC diagnosis is associated with overdiagnosis in cancer survivors. It should also be noted that while overdiagnosis may be easily identifiable at the population level based on review of population data, in the clinical situation, overdiagnosis at the individual patient level would be difficult to ascertain. This situation reflects a tension between system level and individual needs.
- Chapters 4 and 5 indicated that increased incidence and mortality risk of MPCs following specific first cancers *might* also be an adverse late effect of the treatment of first cancer. Previous studies have reported the risk of MPCs following specific treatments of different first cancers. However, the risks varied across countries and evidence from Australian data is limited. In addition, treatment for cancer is rapidly evolving, thus findings from historical data may not be generalizable to individuals with more recent cancer diagnoses. Current treatment data (procedures and dosage) is therefore needed to assess associations between treatment and the development of

MPCs in Australians with a first cancer diagnosis. Data linkage between the TCR database and Tasmanian public hospital radiation oncology database could advance our understanding of these associations between first cancer treatment and the development of MPCs and corresponding mortality.

- Given the finding of increased mortality risks due to specific non-cancer events in Chapter 6, it is important to assess the relationship between cancer treatment and development of fatal non-cancer events, and/or if cancer treatment aggravates pre-existing non-cancer disease. These findings will help optimise follow-up guidelines for cancer and otherwise improve supportive care after a cancer diagnosis.
- Findings in this thesis have indicated that cancer patients are now facing a higher and increasing risk of developing MPCs, and are at risk of death from their MPCs. Further, with improved cancer survivorship and the aging population, there will be an increasing number of individuals living with MPCs. Individuals with one cancer diagnosis may experience a number of psychological problems [15], thus individuals with MPCs could be expected to have more severe psychological impacts. A recent systematic review identified only five studies that have reported psychological distress among MPC survivors [16], revealing a striking paucity of research on this topic. Future studies are required to enable firm conclusions to be drawn on the comparative impacts of psychological distress among MPC survivors, and to identify psychosocial needs in this population.

7.6 Conclusion

The series of studies presented in this thesis have together revealed that the risk of developing MPCs has increased since the 1980s, and that the mortality risk due to MPCs became elevated during a period in which there was an increased detection of non-fatal first cancers.

CVD was the leading cause of competing mortality among patients with a first cancer diagnosed during 2006-2013, with increased mortality risks due to non-cancer events mostly observed within one year of cancer diagnosis. These findings add to current literature to inform clinicians and cancer patients about the current risk of MPC development, competing mortality risks, and provide a robust, unbiased and comprehensive evidence-base to help optimise current clinical guidelines for follow-up strategies after a cancer diagnosis. The work undertaken in this thesis will be of importance in directing future research on investigating the mode of MPC diagnosis, evaluating the benefits and harms of medical investigations and cancer treatment, and supporting the necessity of identifying psychosocial needs of individuals living with MPCs.

7.7 References

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